PCT/GB00/02502

09[redacted]92671

GB00/2302

INVESTOR IN PEOPLE

The Patent Office

4

PRIORITY DOCUMENT

SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

REC'D 10 AUG 2000

WIPO PCT

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

10 AUG 2000

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

I also certify that by virtue of an assignment registered under the Patents Act 1977, the application is now proceeding in the name as substituted.

I also certify that the attached copy of the request for grant of a Patent (Form 1/77) bears an amendment, effected by this office, following a request by the applicant and agreed to by the Comptroller-General.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

Signed Andrew Gersey

Dated 13 July 2000

The Patent Office

GB9929553.7

By virtue of a direction given under Section 30 of the Patents Act 1977, the application is proceeding in the name of
PROTHERICS MOLECULAR DESIGN LIMITED,
Beechwood House,
Lyme Green Business Park,
Macclesfield,
Cheshire,
SK11 0JL,
United Kingdom

[ADP No. 07935026001]

THE PATENT OFFICE
C
14 DEC 1999
LONDON

15DEC99 E499297-1 D00027
P01/7700 0.00-9929553.7

Patents Form 1/77

Patents Act 1977
(Rule 16)

The Patent Office

1/77

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office
Cardiff Road
Newport
Gwent NP9 1RH

1.	Your reference	44.3.70304/004
2.	Patent application number *(The Patent Office will fill in this part)*	**9929553.7**
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	Proteus Molecular Design Limited Beechfield House Lyme Green Business Park Macclesfield Cheshire SK11 0JL
	Patents ADP number *(if you know it)*	5653144002
	If the applicant is a corporate body, give country/state of incorporation	UK
4.	Title of the invention	Compounds
5.	Name of your agent *(if you have one)*	~~Frank B. Dehn & Co.~~ Marks & Clerk
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	~~179 Queen Victoria Street London EC4V 4EL~~ Sussex House, 83-85 Mosley St, Manchester M2 3LG
	Patents ADP number *(if you know it)*	~~166001~~ 18004
6.	If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country / Priority application number *(if you know it)* / Date of filing *(day / month / year)*
7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application / Date of filing *(day / month / year)*
8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if: a) any applicant named in part 3 is not an inventor, or b) there is an inventor who is not named as an applicant, or c) any named applicant is a corporate body. See note (d))*	yes

SECTION 30 (1977 ACT) APPLICATION FILED 21-06-00

FS1/77 5/6/2000

9.	**Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document**	
	Continuation sheets of this form	-
	Description	61
	Claim*(s)*	-
	Abstract	-
	Drawing*(s)*	-
10.	**If you are also filing any of the following, state how many against each item.**	
	Priority documents	-
	Translations of priority documents	-
	Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	-
	Request for preliminary examination and search *(Patents Form 9/77)*	-
	Request for substantive examination *(Patents Form 10/77)*	-
	Any other documents *(please specify)*	-
11.		**I/We request the grant of a patent on the basis of this application.**
		Signature Frank B Dehn & Co **Date** 14 December 1999
12.	**Name and daytime telephone number of person to contact in the United Kingdom**	Julian Cockbain 020 7206 0600

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) *If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.*
b) *Write your answers in capital letters using black ink or you may type them.*
c) *If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s) of the form. Any continuation sheet should be attached to this form.*
d) *If you have answered 'Yes', Patents Form 7/77 will need to be filed.*
e) *Once you have filled in the form you must remember to sign and date it.*
f) *For details of the fee and ways to pay please contact the Patent Office.*

70304/004.607

Compounds

This invention relates to compounds which are inhibitors of serine proteases and to pharmaceutical compositions thereof and their use in the treatment of the human or animal body.

The serine proteases are a group of proteolytic enzymes which have a common catalytic mechanism characterized by a particularly reactive Ser residue. Examples of serine proteases include trypsin, tryptase, chymotrypsin, elastase, thrombin, plasmin, kallikrein, Complement C1, acrosomal protease, lysosomal protease, cocoonase, α-lytic protease, protease A, protease B, serine carboxypeptidase II, subtilisin, urokinase, Factor VIIa, Factor IXa, and Factor Xa. The serine proteases have been investigated extensively over a period of several decades and the therapeutic value of inhibitors of serine proteases is well understood.

Serine protease inhibitors play a central role in the regulation of a wide variety of physiological process including coagulation, fibrinolysis, fertilization, development, malignancy, neuromuscular patterning and inflammation. It is well known that these compounds inhibit a variety of circulating proteases as well as proteases that are activated or released in tissue. It is also becoming clear that serine protease inhibitors inhibit critical cellular processes, such as adhesion, migration, free radical production and apoptosis. In addition, animal experiments indicate that intravenously administered serine protease inhibitors, variants or cells expressing serine protease inhibitors, provide a protective effect against tissue damage.

Serine protease inhibitors have also been predicted to have potential beneficial uses in the treatment of disease in a wide variety of clinical areas such as

oncology, neurology, haematology, pulmonary medicine, immunology, inflammation and infectious disease.

In particular serine protease inhibitors may be beneficial in the treatment of thrombotic diseases, asthma, emphysema, cirrhosis, arthritis, carcinoma, melanoma, restenois, atheroma, trauma, shock and reperfusion injury.

Thus for example an inhibitor of Factor Xa has value as a therapeutic agent as an anticoagulant, e.g. in the treatment and prevention of thrombotic disorders. The use of a Factor Xa inhibitor as an anticoagulant is desirable in view of the selectivity of its effect. Many clinically approved anticoagulants have been associated with adverse events owing to the non-specific nature of their effects on the coagulation cascade.

Also, there are well-known associations of $\alpha 1$ protease inhibitor deficiency with emphysema and cirrhosis and C1 esterase inhibitor deficiency with angioedema.

We have now found that certain aromatic compounds carrying bulky lipophilic side chains are particularly effective as inhibitors of serine proteases, especially proteases with negatively charged P1 specificity pockets, and most especially the serine proteases thrombin, trypsin, urokinase, Factor VIIa and most importantly Factor Xa. The Factor Xa inhibitors of this invention are potentially useful for the prophylaxis or treatment of thrombotic disorders such as amongst others venous thrombosis, pulmonary embolism, arterial thrombosis, myocardial ischaemia, myocardial infarction, and cerebral thrombosis. They potentially have benefit in the treatment of acute vessel closure associated with thrombolytic therapy and restenosis, e.g. after transluminal coronary angioplasty or bypass grafting of the coronary or peripheral arteries and in the maintenance of vascular access patency in long term hemodialysis patients.

Factor Xa inhibitors of this invention may, with benefit, form part of a combination therapy with an anticoagulant with a different mode of action or with a thrombolytic agent.

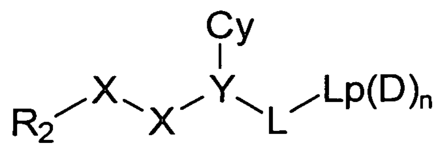
Hence, the invention also comprises certain compounds which have been found to be inhibitors of both Factor Xa and thrombin. These compounds have excellent potential therapeutic value and may synergistically boost Fxa antithrombotic effect.

We have previously reported in WO99/11657 and WO99/11658 that certain benzamidine and isoquinoline derivatives carrying a bulky lipophilic side chain are excellent inhibitors of serine proteases. Surprisingly, we have now found certain other aromatic compounds also show inhibitory activity against serine proteases, in particular Factor Xa, despite the lack of the amidino or 1-aminoisoquinoline functionality previously believed to be crucial for activity as a factor Xa inhibitor.

The compounds of the invention are thus likely to be available for administration orally. Also, it has been found that the compounds of the invention perform excellently in the prothrombin time assay (PT) when compared to aminoisoquinolines of similar factor Xa activity. The PT assay is a coagulation assay and it is widely accepted that direct acting Factor Xa inhibitors which perform well in the PT assay are more likely to be good antithrombotics.

In WO99/09053 certain 2-aminobenzamide compounds are disclosed as potential motilin receptor antagonists and in US 3268513 similar 2-aminobenzamide compounds are suggested as potential antibacterial agents. However, the novel compounds of the present invention have not before been suggested as potential serine protease inhibitors.

Thus viewed from an one aspect the invention provides a serine protease inhibitor compound of formula (I)



(I)

(where R_2 represents a 5 or 6 membered aromatic carbon ring optionally interrupted by a nitrogen, oxygen or sulphur ring atom, optionally being substituted in the 3 and/or 4 position by halo, nitro, haloalkoxy, amino, cyano, haloalkyl, alkylthio, alkenyl, alkynyl, acylamino, tri or difluromethoxy, carboxy, acyloxy, $MeSO_2$- or R_1 or the substituents at the 3 and 4 positions taken together form a fused ring which is a 5 or 6 membered carbocyclic or heterocyclic ring optionally substituted by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R_1, and optionally substituted in the position alpha to the X-X.. group (i.e. 6 position for a six membered aromatic ring etc) by amino, hydroxy, halo, alkyl, carboxy, cyano, amido, aminoalkyl, alkoxy or alkylthio with the proviso that R_2 cannot be isoquinolyl;

each X independently is a C, N, O or S atom or a CO, CR_1, $C(R_1)_2$ or NR_1 group, at least one X being C, CO, CR_1 or $C(R_1)_2$;

each R_1 independently represents hydrogen or hydroxyl, alkoxy, alkyl, aminoalkyl, hydroxyalkyl alkoxyalkyl, alkoxycarbonyl, acyloxymethoxycarbonyl or alkylamino optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl;

L is an organic linker group containing 1 to 5 backbone atoms selected from C, N, O and S, or a branched alkyl or cyclic group;

Y (the α-atom) is a nitrogen atom or a CR_1 group or Y and L taken together form a cyclic group;

Cy is a saturated or unsaturated, mono or poly cyclic, homo or heterocyclic group, preferably

containing 5 to 10 ring atoms and optionally substituted by groups R_3 or phenyl optionally substituted by R_3;

each R_3 independently is R_1, amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, triazolyl, imidazolyl, tetrazolyl, hydrazido, alkyl imidazolyl, thiazolyl, alkyl thiazolyl, alkyl oxazolyl, oxazolyl, alkylsulphonamido, alkylamino-sulphonyl, aminosulphonyl, haloalkoxy and haloalkyl;

Lp is a lipophilic organic group, e.g. an alkyl, heterocyclic, alkenyl, alkaryl, cycloalkyl, polycycloalkyl, cycloalkenyl, aryl, aralkyl or haloalkyl group or a combination of two or more such groups optionally substituted by one or more of oxa, oxo, aza, thia, or R_3 groups, preferably a group containing up to 25 carbon atoms;

D is a hydrogen bond donor group; and n is 0, 1 or 2);

or a physiologically tolerable salt thereof, e.g. a halide, phosphate or sulphate salt or a salt with ammonium or an organic amine such as ethylamine or meglumine.

In the compounds of the invention, where the alpha atom is carbon it preferably has the conformation that would result from construction from a D-α-aminoacid NH_2-CR_1(Cy)-COOH where the NH_2 represents part of X-X. Likewise the fourth substituent R_1 at an alpha carbon is preferably a methyl or hydroxymethyl group or hydrogen.

In the compounds of the invention, unless otherwise indicated, aryl groups preferably contain 5 to 10 ring atoms optionally including 1, 2 or 3 heteroatoms selected from O, N and S; alkyl, alkenyl or alkynyl groups or alkylene moieties preferably contain up to 6 carbons, e.g. C_{1-6} or C_{1-3}; cyclic groups preferably have ring sizes of 3 to 8 atoms; and fused multicyclic groups preferably contain 8 to 16 ring atoms.

The linker group from the R_2 group to the alpha atom is preferably selected from -CH=CH-, -CONH-, -$CONR_1$-, -

NH-CO-, -NH-CH_2-, -CH_2-NH-, -CH_2O-, -OCH_2-, -COO-, -OC=O- and -CH_2CH_2-. Preferably, the X moiety nearest to the alpha atom is an NH or O atom, most preferably a NH group. The X moiety alpha to the aromatic ring is preferably a carbon based group such as CH_2 or CO, preferably CO. Thus a particularly preferred linker X-X is -CONH-. In an alternative embodiment the linker is preferably a -OCH_2- group.

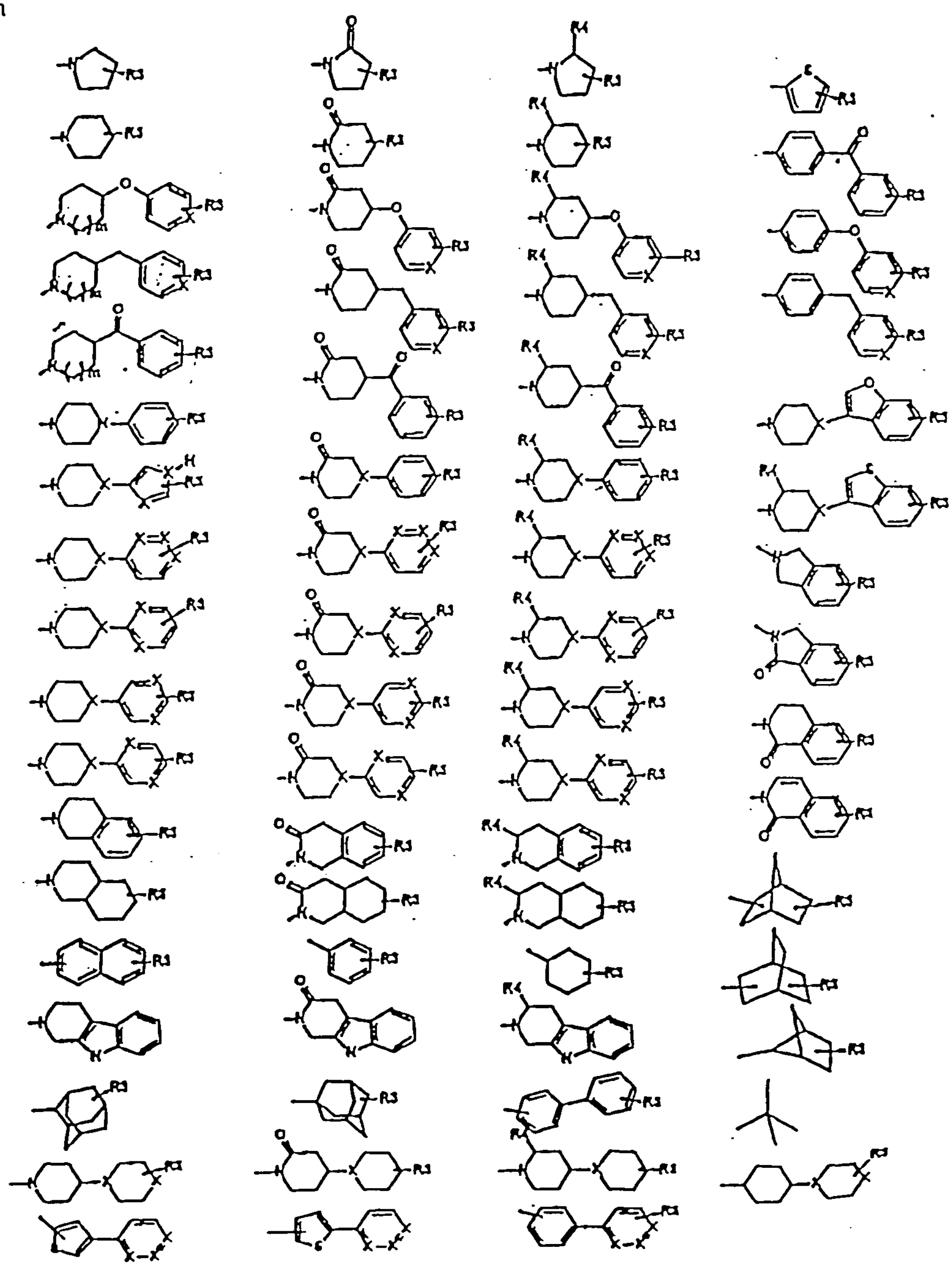
The alpha atom (Y) is preferably a CH or $C(CH_3)$ group, especially CH.

The linker group from the alpha atom to the lipophilic group is preferably CO, CH_2NH, $CONR_1(CH_2)_m$, $(CH_2)_mN(R_1)CO(CH_2)_m$, $(CH_2)_{m+2}$, $CO(CH_2)_m$, $(CH_2)_mCO$, $(CH_2)_mOC{=}O$, $(CH_2)_mO$, $CH{=}CH(CH_2)_m$, SO_2, SO_2NR_1, $SO_2(CH_2)_m$, $(CH_2)_mSO_2$ or $(CH_2)_mSO_2NR_1$ (where each m is independently 0 or 1). The linker may be optionally branched, for example, to incorporate a polar functionality. In a preferred embodiment Y and L taken together form a cyclic group and the alpha atom is therefore a carbon atom. The cyclic group can be unsubstituted or substituted and can have a ring size of from 3 to 8 atoms. Preferably, the cyclic group is a cyclic amide, most preferably wherein the amide nitrogen of the cyclic amide group is bound to the lipophilic group.

The lipophilic group preferably comprises a cycloalkyl, azacycloalkyl, diazacycloalkyl, phenyl, naphthyl, adamantyl, decalinyl, tetrahydrodecalinyl, bicycloalkyl, mono- or diazabicycloalkyl, mono- or bicyclo heteroaromatic or a linear or branched alkyl, alkylene, alkenyl or alkenylene group all optionally substituted by one or more groups R_3, or a combination of at least two such groups linked by a spiro linkage or a single or double bond or by C=O, O, S, SO, SO_2, $CONR_1$, NR_1-CO-, NR_1 linkage. For example, representative lipophilic groups include a methyl-cyclohexyl, methylcyclohexylmethyl, methylphenylmethyl, phenylethyl, benzylpiperidinyl, benzoylpiperidinyl, bispiperidinyl or

phenylpiperazinyl.

Most preferably, the lipophilic group is selected from



wherein R_3 is as hereinbefore defined;

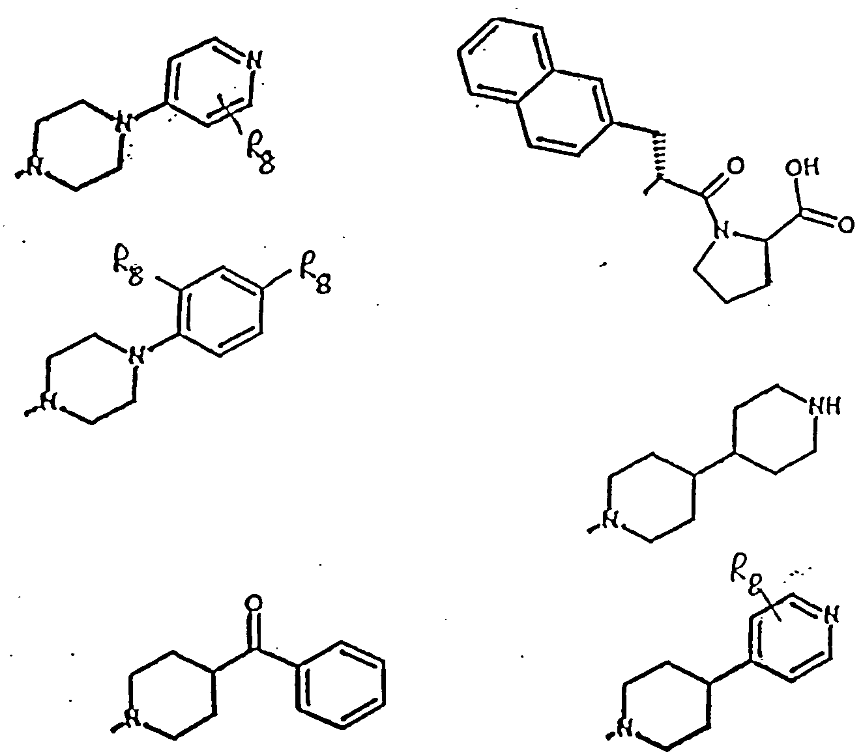
m represents 0 or 1;

R_4 represents hydrogen, $(CH_2)_wCOOH$, $(CH_2)_wCONH_2$, $(CH_2)_wCON\alpha$-AminoAcid;

w represents an integer from 0 to 4; and

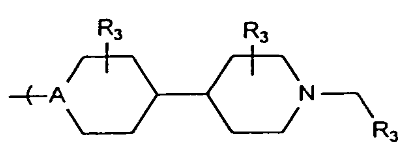
X represents CH or N.

For example specific lipophilic groups include



especially when R_8 represents H, OMe, SO_2Me, F, NO_2, $SO_2N(R_1)_2$, Cl, OH or a 5 membered heterocyclic group.

Another highly preferred lipophilic group is of formula (DP)

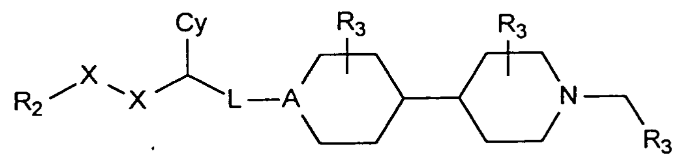


(DP)

wherein A represents N or CH and R_3 is as

hereinbefore defined. When the lipophilic group is (DP) it is preferred that the group L represents CO, CH_2 or SO_2. Also, it is preferred if the R_3 groups in the formula DP are hydrogen.

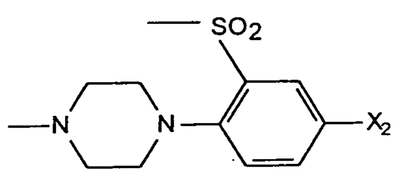
Hence, preferred compounds of the invention are those of formula (J)



(J)

where R_2, X-X, and Cy are as hereinbefore defined and L represents CO, CH_2 or SO_2.

Another highly preferred lipophilic group is based on the formula (K)



(K)

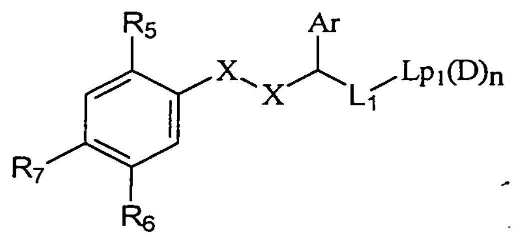
wherein X_2 is halo, hydrogen, amino, nitro or $CONH_2$. Preferably X_2 is fluoro. Compounds in which the lipophilic group is based on the formula (K) or (J) have been found to perform particularly well in the prothrombin time assay.

The hydrogen bond donor group which may be attached to the lipophilic group preferably has a nitrogen or oxygen atom as the donor atom and conveniently is a hydroxyl group, a primary, secondary or tertiary amine, or a primary or secondary imine group (as part of an amidine or guanidine) or a saturated or unsaturated heterocyclic group containing a ring nitrogen, preferably a group containing 5 to 7 ring atoms. Where the donor atom is a ring nitrogen, the remote portion of the heterocyclic ring may be part of the lipophilic

group.

The cyclic group attached to the alpha carbon is preferably an optionally R_3 substituted phenyl, thienyl or naphthyl group.

In one embodiment the aromatic R_2 group is an optionally substituted phenyl, naphthyl, indolyl or isoindolyl group and accordingly, preferred compounds of the invention are of formula (II)



(II)

(wherein R_5 is amino, hydroxy or hydrogen, and R_6 and R_7 which may be the same or different represent halo, nitro, thiol, cyano, haloalkyl, haloalkoxy, amido, hydrazido, amino, alkylthio, alkenyl, alkynyl or R_1 or taken together form a 5 or 6 membered fused carbocyclic ring or 5 membered heterocyclic ring, which may itself be substituted by R_1, amino, halo, cyano, nitro, thiol, alkylthio, haloalkyl, haloalkoxy.

Ar is an unsubstituted or substituted aryl group, preferably phenyl;

X-X is -CONH-, $-CH_2CH_2-$, CH_2O-, -COO-, $-CH_2NH-$, $-OCH_2-$ or $-NHCH_2-$, especially -CONH-;

L_1 is a valence bond or an organic linker group containing 1 to 4 backbone atoms selected from C, N, O and S;

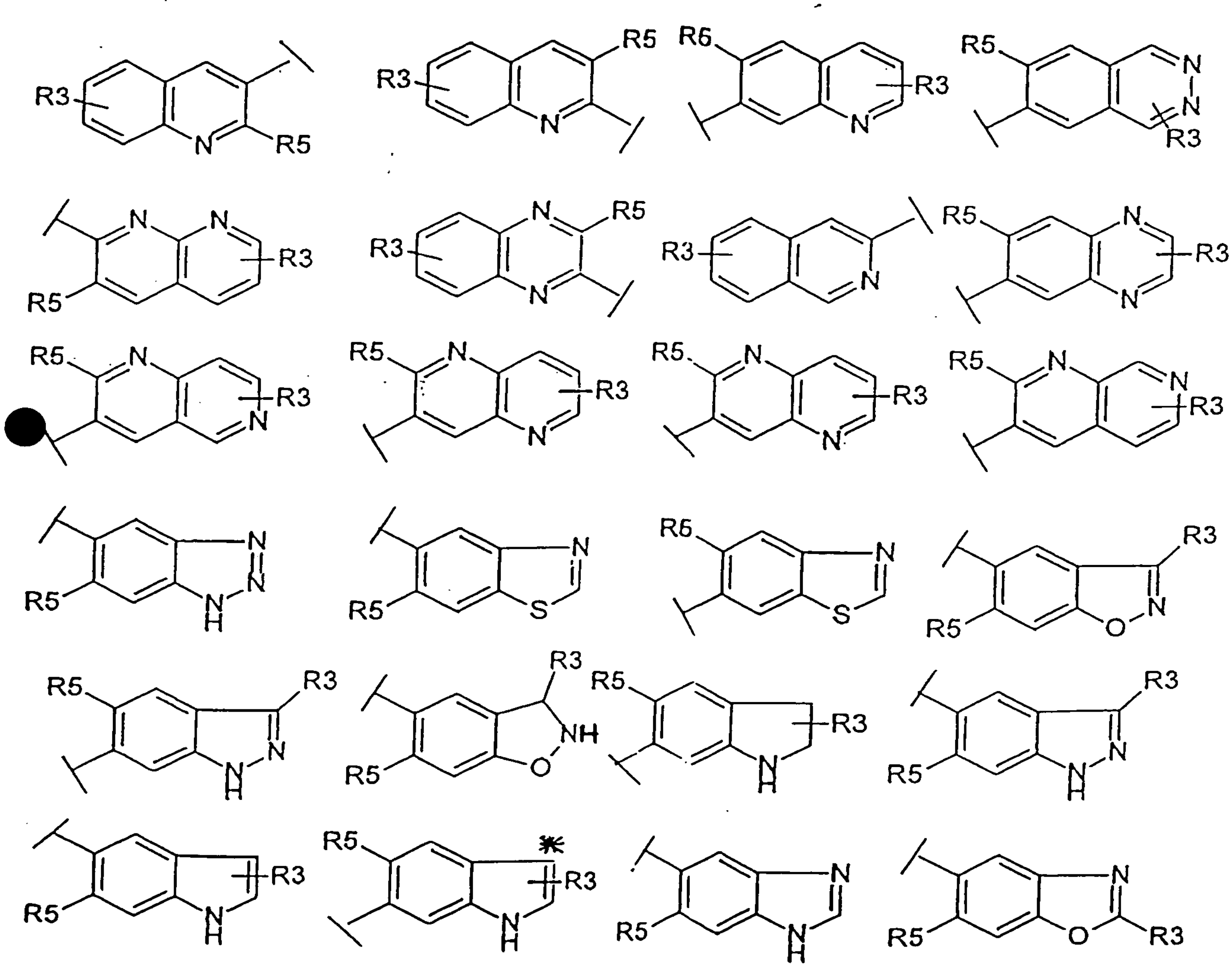
Lp_1 is a cycloalkyl, azacycloalkyl, diazacycloalkyl, phenyl, naphthyl, adamantyl, decalinyl, tetrahydrodecalinyl, bicycloalkyl, mono- or diazabicycloalkyl, mono- or bicyclo heteroaromatic or a linear or branched alkyl, alkylene, alkenyl or alkenylene group all optionally substituted by a group R_3, or a combination of at least two such groups linked

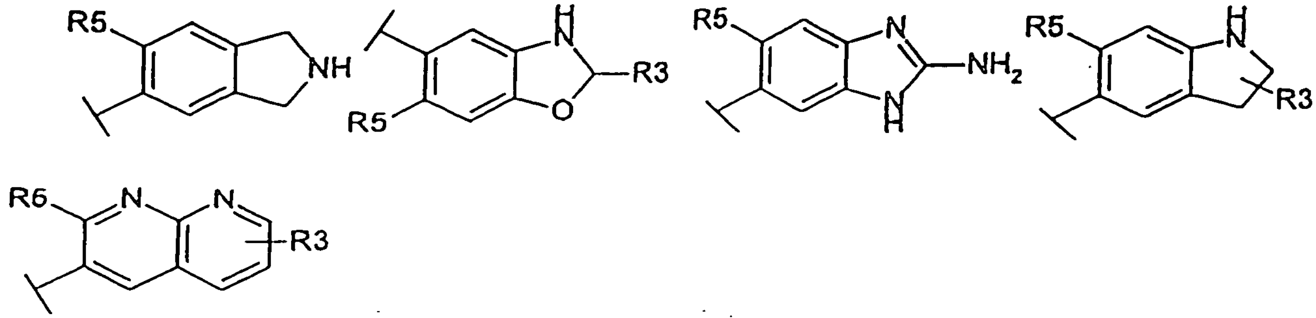
by a spiro linkage or a single or double bond or by C=O, O, S, SO, SO_2, $CONR_1$, NR_1-CO-, NR_1 linkage. For example, representative lipophilic groups include a methyl-cyclohexyl, methylcyclohexylmethyl, bispiperidinyl, methylphenylmethyl, phenylethyl, benzylpiperidinyl, benzoylpiperidinyl or phenylpiperazinyl and those as hereinbefore described;

D is a hydrogen bond donor group;

and n is 0, 1 or 2).

In an alternative embodiment the phenyl derivative forming part of the R_2 functionality may instead be a nitrogen heterocyclic group, e.g. pyridine. Thus suitable R_2 groups may be



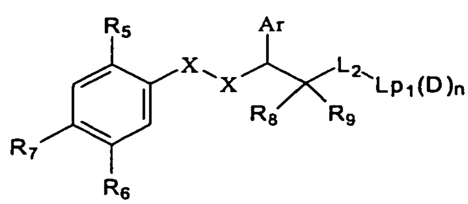


In a particulalrly favoured embodiment the R_2 group is an indole as marked by a * above in which R_5 is hydrogen and R_3 is a hydrogen or halogen present at the 3 position.

It is preferred that at least one of R_6 and R_7 be other than hydrogen and that R_6, if present, is preferably a substituent containing one or more polar hydrogens such as hydroxy, amino, alkylamino, aminoalkyl, alkylaminoalkyl, aminocarbonyl, alkylaminocarbonyl, alkylcarboxyamino, hydrazo and alkylhydrazo; alternatively R_6 and R_7 are joined together in the formation of a naphthyl or indolyl or azaindolyl or diazaindolyl group.

It is especially preferred that R_6 be amino and R_7 be chloro, bromo, methyl, methoxy or vinyl; or that R_6 and R_7 taken together form an indolyl ring with the NH at the 6-position or taken together form a naphthyl ring.

In a further preferred embodiment the compounds of the invention are of formula (A)



(A)

(wherein R_5, R_6, R_7, Ar, X-X, Lp_1, D_n are as hereinbefore defined; L_2 is a valence bond or an organic linker group containing 1 to 3 backbone atoms selected

from C, N, O and S and R_8 and R_9 are hydrogen or taken together with the carbon atom to which they are attached form a carbonyl group). Again, in an alternative embodiment the phenyl derivative forming part of the R_2 functionality may instead be a nitrogen heterocyclic group, e.g. pyridine.

In one embodiment, L_2 comprises the backbone of an alpha amino acid, the lipophilic group being the side chain of the amino acid. The carboxyl part of the alpha amino acid may be optionally coupled via an amide bond to an amino acid or to a primary or secondary cyclic or acyclic alkyl amine or diamine or via an ester bond to primary or secondary alcohols.

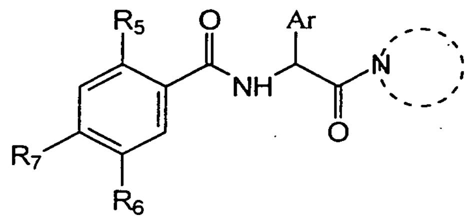
In one preferred embodiment R_8 and R_9 are hydrogen and L_2 is a OC=O or NHC=O group.

In a preferred embodiment, L_2 represents a valence bond and the lipophilic group is bound directly to a carbonyl alpha to the alpha atom via a nitrogen atom which forms part of the lipophilic group. Suitable lipophilic groups in this case therefore include piperidinyl, pyrrolidinyl and piperazinyl. In a preferred embodiment the piperidine or piperazinyl group is further substituted by a phenyl, benzyl, phenoxy, piperidine, pyridine or benzoyl group, optionally substituted on the phenyl ring by one or more R_3 groups. In a more preferred embodiment a piperazine is substituted with a phenyl group substituted at the 2-position with an electron withdrawing group such as fluoro, nitro, triazolyl, cyano, alkoxycarbonyl, aminocarbonyl, aminosulphonyl, alkylaminosulphonyl and, especially preferred, alkylsulphonyl; and, at the 4-position, with hydrogen, fluoro, alkoxy or hydroxy. In another more preferred embodiment a piperidine is substituted at the 4-position with 4-piperidine which itself may be substituted on nitrogen by alkyl or aminocarbonylalkyl or alkylaminocarbonyl alkyl.

In a further embodiment, the lipophilic group has

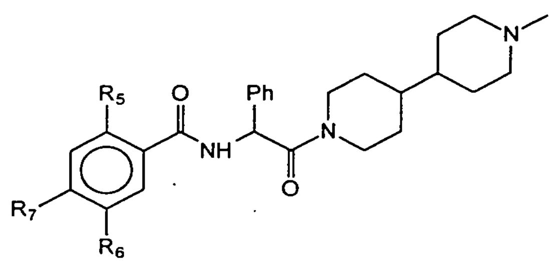
attached a group of the formula $-COOR_1$ or -CON-aminoacid or ester derivative thereof.

Particularly preferred compounds are those of formula (G)



(G)

(wherein Ar, R_6 and R_7 are as hereinbefore defined, R_5 represents hydrogen or amino and ----- represents a cyclic group) or of formula (H)

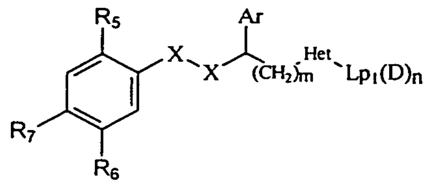


(H)

(wherein R_6 and R_7 are as hereinbefore defined, and R_5 represents hydrogen or amino). In a preferred embodiment R_6 is amino and R_7 a halogen, especially chlorine.

Again, in an alternative embodiment the phenyl derivative forming part of the R_2 functionality in formulae (G) and (H) may instead be a nitrogen heterocyclic group, e.g. pyridine, indole.

In another embodiment the group binding the alpha carbon atom to the lipophilic group comprises a heterocyclic group. Accordingly, preferred compounds of the invention also include those of formula (III)



(III)

(wherein R_5, R_6, R_7, Ar, X-X, Lp_1, D_n are as hereinbefore defined;

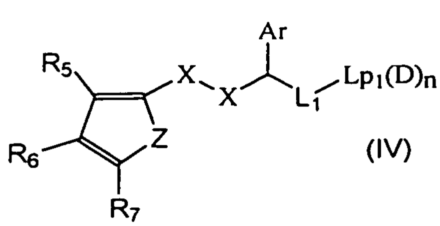
m is 0, 1 or 2;

Het is a 5 or 6-membered heterocyclic group interrupted by 1, 2 or 3 heteroatoms selected from O, N and S optionally substituted by a group R_3). Again, in an alternative embodiment the phenyl derivative forming part of the R_2 functionality may instead be a nitrogen heterocyclic group, e.g. pyridine.

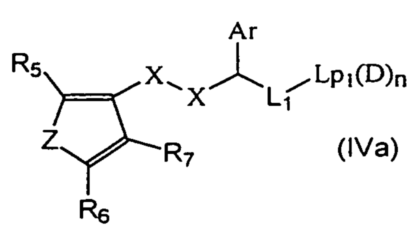
Where Het is a five membered ring, the two ring atoms at which it is connected are preferably separated by one ring atom. Where Het is a six-membered ring, the two ring atoms at which it is connected are preferably separated by one or two ring atoms. Representative heterocyclic groups include thiazole, oxazole, oxadiazole, triazole, thiadiazole or imidazole. Where the heterocyclic group is substituted by R_3 this is preferably a COOH or $COOR_1$ connected to the heterocycle via a valence bond or alkylene chain.

In a further embodiment, the lipophilic group has attached a group of the formula $-COOR_1$ or -CON-aminoacid or ester derivative thereof.

In an alternative embodiment, the main aromatic R_2 ring in the compounds of the invention is a five membered aromatic ring leading to compounds of formula (IV) or (IVa)

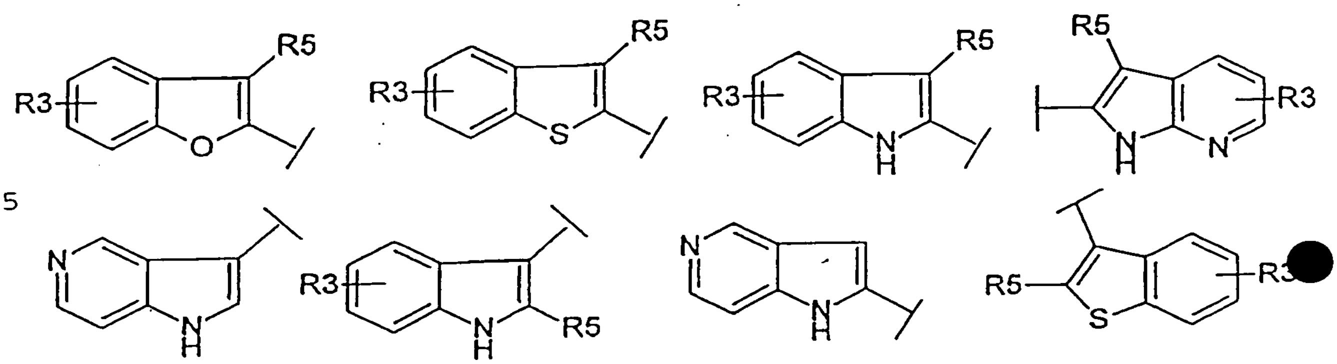


(IV)

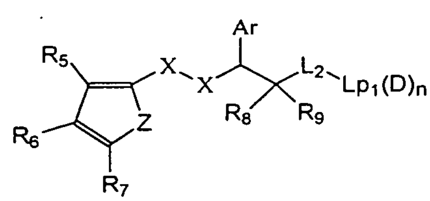
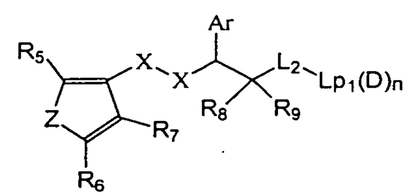


(IVa)

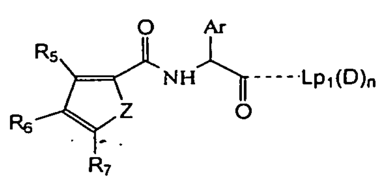
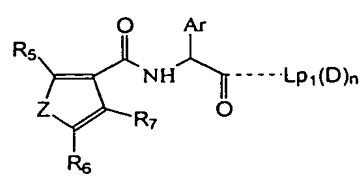
(wherein R_5, R_6, R_7, X-X, Ar, L_1, Lp_1, D and n are as hereinbefore described for formula (II) and Z represents N, O or S). It is preferred that at least one of R_6 and R_7 be other than hydrogen, or that R_6 and R_7 taken together enable the formation of an indolyl, or azaindolyl group or diazaindolyl group. Preferences for other substituents are as for formula (A) above. Examples of possible fused systems are given below.



Hence in a preferred embodiment the compounds of the invention are of formula C or D

(C)   (D)

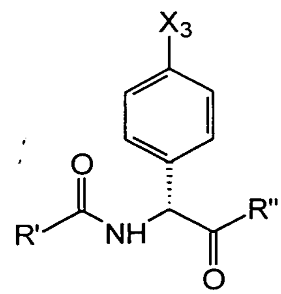
(wherein R_5, R_6, R_7, Ar, X-X, Z, R_8, R_9, L_2 Lp_1, D_n are as hereinbefore defined) preferences for Ar, X-X, R_8, R_9, L_2 Lp_1, D_n are as for formula (A) above; or compounds of formula E or F:

(E)   (F)

(wherein Lp_1 is connected to the carbonyl via a nitrogen atom, R_6, R_7, Ar, Z, Lp_1, D_n are as hereinbefore defined

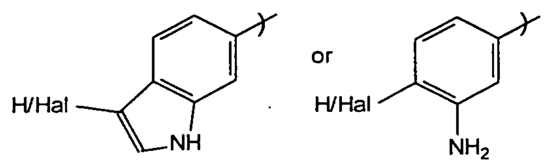
and R_5 is hydrogen or amino) preferences for Ar, Lp_1, D_n are as for formula (A) above.

As previously mentioned, a number of compounds of the invention have been found to be excellent mixed inhibitors in that they inhibit both the serine proteases Factor Xa and thrombin. Such mixed inhibitors are preferably based on the formula (L)

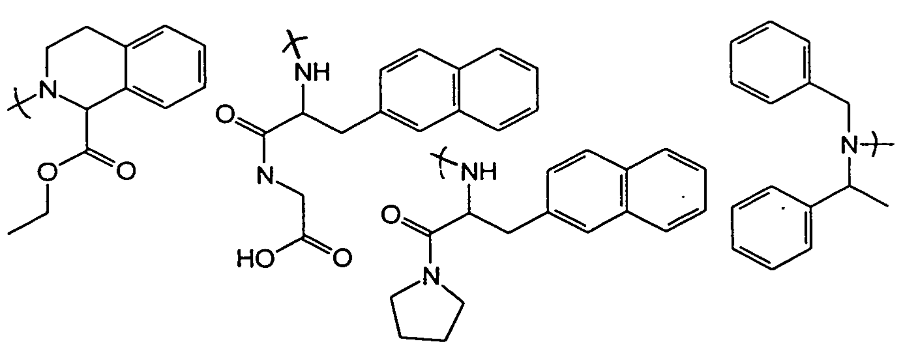


(L)

wherein R' represents



X_3 represents hydrogen or a polar group such as amino or $CONH_2$, especially $CONH_2$; and
R" represents a cyclic group bound to the carbonyl by a nitrogen atom or an optionally substituted group of formula



The compounds of the invention may be prepared by conventional chemical synthetic routes, e.g. by amide bond formation to couple the aromatic function to the alpha atom and to couple the lipophilic function to the alpha atom. Where the alpha atom is a carbon, the cyclic group-alpha atom combination may conveniently derive from an alpha amino acid with the aromatic deriving from for example an acid derivative of a compound based on R_2, e.g. o-amino-benzoic acid. Amide formation from such reagents (in which any amino or hydroxyl function may if desired be protected during some or all of the synthesis steps) yields a compound of formula (V).

$$R_2\text{-CONH-CH(Cy)-COOH} \qquad (V)$$

(where Cy and R_2 are as defined above).

The lipophilic group (and optionally simultaneously the hydrogen bond donor) may then conveniently be introduced by reaction of a compound of formula (V) (or another analogous carboxylic acid) optionally after transformation into an activated form, e.g. an acid chloride or active ester, with a lipophilic group carrying an amine, hydroxylamine, hydrazine or hydroxyl group, e.g. to produce compounds with linkages of -CO-NR_1-, -CO-NR_1-O-, -CO-NR_1-NR_1- and -CO-O- from the alpha atom (where it is a carbon) to the lipophilic group. Where Y and L taken together form a cyclic amide group the lipophilic group can be conveniently introduced by reacting the compound of formula (V) with a lipophilic group carrying a secondary amine with an active side chain. Cyclisation can be base induced via nucleophilic attack of the alpha atom on a leaving group on the active side chain. If necessary the amide linkage can be reduced using an appropriate reducing agent employing the necessary protection depending on whether concurrent reduction of the carboxylic acid moiety is also desired.

Alternatively a compound of formula V or another analogous carboxylic acid may be transformed into an alcohol by reaction with isobutylchloroformate and reduction with sodium borohydride.

Such an alcohol, e.g. of formula VI

$$R_2 - CONH - CH(Cy)CH_2OH \qquad (VI),$$

can be reacted to introduce the lipophilic group by reactions such as:

alkylation with an alkyl halide in the presence of a base;

reaction with diethyl azodicarboxylate/triphenylphosphine and a hydroxylated aryl compound;

by reaction with an activated carboxylic acid (e.g. an acid chloride) or with a carboxylic acid and diethylazodicarboxylate/triphenylphosphine;

by reaction with an isocyanate; and

by treatment with methanesulphonyl chloride or trifluoromethanesulphonic anhydride and reaction with an amine, or with a thiol optionally followed by oxidation, e.g. with potassium metaperiodate or hydrogen peroxide.

In this way compounds with linkages of $-CH_2-O-$, $-CH_2-O-CO-$, $-CH_2-O-CO-NR_1-$, $-CH_2-NR_1-$, $-CH_2-S-$, $-CH_2-SO-$ and $-CH_2-SO_2-$ between the alpha carbon and the lipophilic group may be produced.

Alternatively the alcohol can be oxidized to form a corresponding aldehyde (e.g. by oxidation with manganese dioxide or DMSO/oxalyl chloride or DMSO/SO_3 or Dess-Martin reagent) which may be reacted to introduce the lipophilic group by reactions such as:

reaction with Wittig reagents or Horner-Emmons reagents, optionally followed by reduction of the resulting carbon:carbon double bond using H_2/Pd-carbon;

reaction with an organometallic, eg a Grignard reagent, optionally followed by reaction on the

resulting hydroxyl group, such as oxidation (eg with MnO_2, DMSO/oxalyl chloride or Dess-Martin reagent), alkylation (eg with an alkyl halide in the presence of a base in a solvent such as DMF), arylation (eg with diethylazo dicarboxylate/triphenyl phosphine and a hydroxyaryl compound), ester formation (eg with an acid chloride or with a carboxylic acid and diethylazido dicarboxylate/triphenyl phosphine), or carbamate formation (eg with an isocyanate);

by reaction with an amine followed by reduction, e.g. with sodium cyanoborohydride;

by reaction with a hydrazine; or

by reaction with a carbazide.

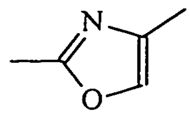
In this way compounds with linkages of $-CH=CR_1-$, $-CH_2-CHR_1-$, $-CHOH-$, $-CHR_1-O-$, $-CHR_1-O-CO-$, $-CHR_1-O-CO-NR_1-$, $-CO-$, $-CH_2-NR_1-$, $-CH=N-NR_1-$ and $-CH=N-NR_1-CO-NR_1-$ between the alpha carbon and the lipophilic group may be produced.

The transformation of alcohol to amine referred to above may be used to produce an amine reagent for lipophilic group introduction, e.g. a compound $R_2-CONH-CH(Cy)-CH_2-NR_1H$.

Such an amine reagent may be reacted to introduce the lipophilic group, e.g. by acylation with an acid halide or activated ester, by reaction with isocyanate, by reaction with an isothiocyanate, or by reaction with a sulphonyl chloride. In this way compounds with linkages of $-CH_2NR_1-CO-$, $-CH_2-NR_1-CO-NR_1-$, $-CH_2NR_1-CS-NR_1-$ and $-CH_2NR_1-SO_2-$ between the alpha carbon and the lipophilic groups may be produced.

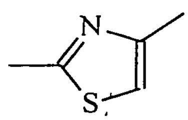
The transformation of acid to amide referred to above may be used to produce an amide reagent for introduction of the lipophilic group, e.g. a compound $R_2-CONH-CH(Cy)-CON(R_1)_2$.

Such amides may be reacted to introduce lipophilic groups, e.g. by reaction with a haloketone (e.g. phenacyl bromide). This provides a linkage

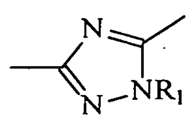


from alpha carbon to lipophilic group.

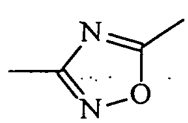
Analogously the amide may be transformed to a thioamide by reaction with Lawesson's reagent and then reacted with a haloketone to form a linkage



The amide reagent may likewise be transformed to a nitrile reagent by dehydration, e.g. with trifluoroacetic anhydride. The nitrile reagent may be reacted with hydrazine then with acyl halide and then cyclized, (e.g. with trifluoroacetic anhydride) to produce a linkage

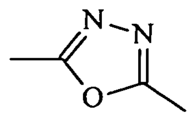


Alternatively it may be treated with hydroxylamine then reacted with acyl halide and cyclized (e.g. with trifluoroacetic anhydride) to produce a linkage



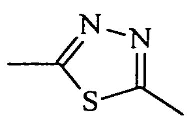
The hydrazide produced by reaction of a carboxylic acid reagent with hydrazine discussed above may likewise be used as a reagent for lipophilic group introduction, e.g. as a compound of formula R_2-CONH-CH(Cy)-CO-NR_1-N$(R_1)_2$.

Thus the hydrazide reagent can be reacted with an acyl halide and cyclized, e.g. with trifluoroacetic anhydride to yield a linkage

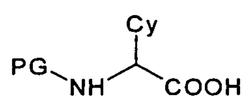


or reacted with an acyl halide or an isocyanate to yield linkages $-CO-NR_1-NR_1-CO-$ and $-CO-NR_1-NR_1-CO-NR_1-$ respectively.

Alternatively the hydrazide may be transformed by reaction with Lawesson's reagent and then reacted with an acyl halide and cyclized (e.g. with trifluoroacetic anhydride) to produce the linkage



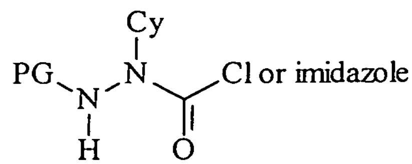
An alternative route to these compounds is to carry out any of the above chemical reactions to incorporate the lipophilic group (an optional H bond donor) into a protected intermediate such as a compound of formula (VII).



PG=Protecting group

The protecting group may then be removed before coupling of the for example o-amino benzoic acid (optionally protected).

A starting reagent for lipophilic group introduction where the alpha atom is nitrogen may be produced for example by reaction of a beta protected hydrazine (such protection to be chosen as to be compatible with the subsequent reagents to be employed) with phosgene, diphosgene, triphosgene or N,N'carbonyl diimidazole to give a reactive compound of the type:



PG = Protecting group

This intermediate may be used as has been described above for the carboxylic starting reagents where the alpha atom is carbon.

Removal of the protecting group by standard methods and coupling with an activated aryl carboxylic acid will give compounds of the type

$$R_2\text{-CONH-N(Cy)-L-Lp(D)}_n$$

(where R_2, X, Y, Cy, L, Lp and D are as defined above).

Thus viewed from a further aspect the invention provides a process for the preparation of a compound according to the invention which process comprises coupling a lipophilic group to a compound of formula (VIII)

$$R_2\text{-(X)}_2\text{-Y(Cy)-}Z_1 \qquad \text{(VIII)}$$

(wherein R_2, X, Y and Cy are as defined above and Z_1 is a reactive functional group), and optionally subsequently coupling a hydrogen bond donor group to said lipophilic group.

The compounds of the invention may be administered by any convenient route, e.g. into the gastrointestinal tract (e.g. rectally or orally), the nose, lungs, musculature or vasculature or transdermally. The compounds may be administered in any convenient administrative form, e.g. tablets, powders, capsules, solutions, dispersions, suspensions, syrups, sprays, suppositories, gels, emulsions, patches etc. Such compositions may contain components conventional in pharmaceutical preparations, e.g. diluents, carriers, pH

modifiers, sweeteners, bulking agents, and further active agents. Preferably the compositions will be sterile and in a solution or suspension form suitable for injection or infusion. Such compositions form a further aspect of the invention.

In particular, it is believed that the compounds of the invention will have excellent oral bioavailability.

Viewed from this aspect the invention provides a pharmaceutical composition comprising a serine protease inhibitor according to the invention together with at least one pharmaceutically acceptable carrier or excipient. The pharmaceutical composition may also optionally comprise at least one further antithrombotic and/or thrombolytic agent.

Viewed from a further aspect the invention provides the use of a serine protease inhibitor according to the invention for the manufacture of a medicament for use in a method of treatment of the human or non-human animal body (e.g. a mammalian, avian or reptilian body) to combat (i.e. treat or prevent) a condition responsive to said inhibitor.

Viewed from a further aspect the invention provides a method of treatment of the human or non-human animal body (e.g. a mammalian, avian or reptilian body) to combat a condition responsive to a serine protease inhibitor (e.g. a condition such as a thrombotic disorder responsive to a factor Xa inhibitor), said method comprising administering to said body an effective amount of a serine protease inhibitor according to the invention.

The dosage of the inhibitor compound of the invention will depend upon the nature and severity of the condition being treated, the administration route and the size and species of the patient. However in general, quantities of from 0.01 to 100 μmol/kg bodyweight will be administered.

All publications referred to herein are hereby

incorporated by reference.

The invention will now be described further with reference to the following non-limiting Examples.

Experimental

Abbreviations used follow IUPAC-IUB nomenclature. Additional abbreviations are Hplc, high-performance liquid chromatography; DMF, dimethylformamide; DCM, dichloromethane; HAOT, 1-hydroxy-7-azabenzotriazole; HATU, [O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate]; Fmoc, 9-Fluorenylmethoxycarbonyl; HOBt, 1-hydroxybenzotriazole; TBTU, 2-(1H-(benzotriazol-1-yl)-1,1,3,3-tetramethyluroniumtetrafluoroborate; EDCI, 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; DIPEA, diisopropylethylamine; Boc, tertiary butyloxycarbonyl; DIPCI, diisopropylcarbodiimide; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; TEA, triethylamine; Rink linker, p-[(R,S)-α-[1-(9H-Fluoren-9-yl)methoxyformamido]-2,4-dimethoxybenzyl]phenyl acetic acid; TFA, trifluoroacetic acid; MALDI-TOF, Matrix assisted laser desorption ionisation - time of flight mass spectrometry, RT, retention time. Unless otherwise indicated amino acid derivatives, resins and coupling reagents were obtained from Novabiochem (Nottingham, UK) and other solvents and reagents from Rathburn (Walkerburn, UK) or Aldrich (Gillingham, UK) and were used without further purification. All solution concentrations are expressed as %Vol./%Vol. unless otherwise stated.

Purification: Purification was by gradient reverse phase Hplc on a Waters Deltaprep 4000 at a flow rate of 50 ml/min. using a Deltapak C18 radial compression column (40 mm x 210 mm, 10-15 mm particle size). Eluant A consisted of aqTFA (0.1%) and eluant B 90% MeCN in

aqTFA(0.1%) with gradient elution (Gradient 1, 0 min. 20%B then 20% to 100% over 36 min., Gradient 2, 0 min. 5%B for 1 min. then 5%B to 20%B over 4 min., then 20% to 60% over 32 min. or Gradient 3, 0 min. 20%B then 20% to 100% over 15 min.). Fractions were analysed by analytical Hplc and MALDI-TOF before pooling those with >95% purity for lyophilisation.

Analysis: Analytical Hplc was on a Shimadzu LC6 gradient system equipped with an autosampler, a variable wavelength detector at flow rates of 0.4 ml/ min. Eluents A and B as for preparative Hplc . Columns used were Techogel15 C18 (2x150mm)(Hplc Technology), Magellan C8 column (2.1x150 mm, 5μm particle size) (Phenomenex))Purified products were further analysed by MALDI-TOF and nmr.

Synthesis of inhibitors

Method 1: Using a solid phase strategy on a Protein Technologies, Symphony Multiple Peptide Synthesiser by attachment of bis amino compounds to Peg-trityl chloride resin: Trityl chloride resin was typically treated with greater than 2 fold excess of the di-amine in dry DCM .The resin was further modified by the attachment of acids. Activation of Fmoc protected amino acid (2-5eq) was by TBTU/ DIPEA, all couplings (minimum 120 min.) were carried out in DMF. Deprotection of the Fmoc group was achieved with 20% piperidine in DMF. In the next stage other acid substituents were added as the HOBt or HOAt esters either by activation with HBTU/HATU or HATU/EDCI with or without Boc protection of amino groups. Cleavage of the products from the resin was by treatment (30 min., ambient) with 10% triethylsilane in TFA, filtration, evaporation and trituration with diethylether.

Synthesis using the Symphony Multiple Peptide Synthesiser.

The Symphony Multiple Peptide Synthesiser is charged with DMF, DCM, TBTU in DMF(450 mM), DIPEA in DMF (900 mM), 20% piperidine in DMF. Resins are held in plastic reaction vessels that allow the introduction of reagents and solvents and nitrogen for agitation or air drying.

A typical synthesis cycle on the Symphony is as follows:-

The reaction vessel containing the resin (0.1 mmol) is charged with the Fmoc protected amino acid (0.5 mmol) and then this is dissolved in DMF (2.5ml), treated with TBTU (0.56 mmol, 1.25ml) and DIPEA (1.1 mmol, 1.25ml) and agitated with nitrogen for 2 hours (agitation times may vary). After coupling the resin is washed with DMF (6x 5ml) then deprotected with 20% piperidine in DMF (2x 5ml for 1 min.each, then 1x 5ml for 8 min.) the resin is then washed with DMF (6x 5ml).

Example 1.
2-Amino-4-chlorobenzoyl-D-phenylglycine 4,4'bispiperidinamide

4,4-Bipiperidine.dihydrochloride (4mmol,1g) was dissolved in water (5ml) and 2M sodium hydroxide solution (10mmol, 5ml) added. The solution was extracted with ethylacetate (2x 50ml) the combined extracts were washed with water, dried over anhydrous sodium carbonate, filtered and evaporated to give the 4,4 bipiperidine (0.35g) as a white solid. The 4,4 bipiperidine was dissolved in dry DMF (2ml) and added to Peg-tritylchloride resin (0.95 mmol/g, 1.5g) pre swollen in dry DCM (10ml). After 2h the resin was washed with DCM (6x5ml), DMF (6x5ml) and DCM (6x5ml). The resin was

then air dried to allow aliquots to be taken.

The 4,4 bipiperidine trityl resin (0.1 mmol) was treated with Fmoc-D-Phenylglycine (0.5 mmol, 187mg), DMF(2.5ml), TBTU in DMF(1.25ml of a 450mM solution) and DIPEA in DMF (1.25ml of a 900 mM solution). The mixture was agitated with nitrogen for 2 hours. Deprotection and washing as above.

A solution of 4-chloroanthranilic acid (87mg 0.5mmole) in dry dimethylformamide (DMF) was treated successively with HOAt (102mg 0.75mmole) and EDCI (115mg 0.6mmole) and stirred at room temperature for 10min. The mixture was transferred to the reaction vessel on the Symphony and agitated for 2 hours with nitrogen. The resin was washed with DMF (6x5ml), DCM (6x5ml) and air dried. The product was cleaved from the resin with 10% triethylsilane in TFA (10ml) for 30 minutes, the resin filtered off and the TFA solution evaporated to dryness and triturated with diethyl ether to give the crude product. The crude product was dissolved in water (10ml), filtered and purified by preparative reverse phase Hplc.

^{1}H nmr (CD_3CN) 7.30 (6H,m); 6.60 (1H,s); 6.55 (1H,d); 5.85 (1H, s); 4.40 (1H,m); 3.75 (1H, m); 2.30-2.95 (6H, m); 1.60 (4H, m); 1.10 (6H, m) MS TOF 456 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 11.77 min.

Example 2.

2-Amino-5-bromobenzoyl-D-phenylglycine 4,4'bispiperidinamide

^{1}H nmr (CD_3CN) 7.30 (7H,m); 6.50 (1H,d); 5.85 (1H, s); 4.40 (1H,m); 3.75 (1H, m); 2.30-2.95 (6H, m); 1.60 (4H, m); 1.10 (6H, m) MS TOF 500 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 11.31 min.

Example 3.

2-Amino-4-methylbenzoyl-D-phenylglycine 4,4'bispiperidinamide

^{1}H nmr (CD_3CN) 7.30 (6H,m); 6.50 (1H,s); 6.45 (1H,d); 5.80 (1H, s); 4.40 (1H,m); 3.75 (1H, m); 2.30-2.95 (6H, m); 2.05 (3H,s); 1.60 (4H, m); 1.10 (6H, m) MS TOF 436 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 9.22 min.

Example 4.

2-Amino-5-methylbenzoyl-D-phenylglycine 4,4'bispiperidinamide

^{1}H nmr (CD_3CN) 7.30 (7H,m); 6.50 (1H,d); 5.85 (1H, s); 4.40 (1H,m); 3.75 (1H, m); 2.30-2.95 (6H, m); 1.60 (4H, m); 1.10 (6H, m). MS TOF 436 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 8.74 min.

Example 5.

2-Amino-5-methoxybenzoyl-D-phenylglycine 4,4'bispiperidinamide

^{1}H nmr (CD_3CN) 7.55 (6H,m); 7.30 (1H,d); 6.95 (1H,m); 6.15 (1H, s); 4.40 (1H,m); 3.75 (1H, m); 3.60 (3H, s); 2.30-2.95 (6H, m); 2.20 (3H, s); 1.60 (4H, m); 1.10 (6H, m) MS TOF 452 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 8.20 min.

Example 6.

2-Dimethylaminobenzoyl-D-phenylglycine 4,4'bispiperidinamide

^{1}H nmr (CD_3CN) 7.80 (1H,d); 7.65 (2H,m); 7.30 (6H,m); 5.85 (1H, s); 4.40 (1H,m); 3.75 (1H, m); 3.10 (6H, s); 2.30-2.95 (6H, m); 1.60 (4H, m); 1.10 (6H, m) MS TOF 450 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 9.57 min.

Example 7.

3-Methylbenzoyl-D-phenylglycine 4,4'bispiperidinamide

^{1}H nmr (CD_3CN) 7.40 (2H,m); 7.30 (7H,m); 5.85 (1H, s); 4.40 (1H,m); 3.75 (1H, m); 2.30-2.95 (6H, m); 2.20 (3H, s); 1.60 (4H, m); 1.10 (6H, m) MS TOF 421 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt

10.68 min.

Example 8.

4-Methylbenzoyl-D-phenylglycine 4,4'bispiperidinamide

^1H nmr (CD_3CN) 7.55 (2H,m); 7.30 (5H,m); 7.10 (2H,m); 5.85 (1H, s); 4.40 (1H,m); 3.75 (1H, m); 2.30-2.95 (6H, m); 2.20 (3H,s); 1.60 (4H, m); 1.10 (6H, m) MS TOF 420 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 10.61 min.

Example 9.

3-Amino-2-naphthoyl-D-phenylglycine 4,4'bispiperidinamide

^1H nmr (CD_3CN) 7.90 (1H,d); 7.60 (1H,d); 7.40 (1H,m); 7.30 (6H,m); 7.05 (1H,m); 6.90 (1H,s); 5.85 (1H, s); 4.40 (1H,m); 3.75 (1H, m); 2.30-2.95 (6H, m); 1.60 (4H, m); 1.10 (6H, m) MS TOF 471 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 9.87 min.

Example 10.

3-Aminobenzoyl-D-phenylglycine 4,4'bispiperidinamide

MS TOF 421 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 9.06 min.

Example 11.

2-Aminobenzoyl-D-phenylglycine 4,4'bispiperidinamide

MS TOF 421 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 9.00 min.

Example 12.

2-Amino-4-fluorobenzoyl-D-phenylglycine 4,4'bispiperidinamide

MS TOF 440 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 9.23 min.

Example 13.

2-Amino-5-fluorobenzoyl-D-phenylglycine 4,4'bispiperidinamide

MS TOF 440 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 9.14 min.

Example 14.

2-Amino-4-nitrobenzoyl-D-phenylglycine 4,4'bispiperidinamide

MS TOF 467 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 10.59 min.

Example 15.

2-Amino-5-nitrobenzoyl-D-phenylglycine 4,4'bispiperidinamide

MS TOF ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 10.57 min.

Example 16.

2-Amino-4,5-dimethoxybenzoyl-D-phenylglycine 4,4'bispiperidinamide

MS TOF 481 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 11.67 min.

Example 17.

Benzoyl-D-phenylglycine 4,4'bispiperidinamide

MS TOF 407 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 9.88 min.

Example 18.

4-Chlorobenzoyl-D-phenylglycine 4,4'bispiperidinamide

MS TOF 441 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 10.89 min.

Example 19.

2-Hydroxybenzoyl-D-phenylglycine 4,4'bispiperidinamide

MS TOF 423 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 8.97 min.

Method 2: By solution phase strategy: Typically an activated Boc-amino acid was treated with an amine (primary or secondary) or alcohol (1eq.). Activation of Boc protected amino acid was by HATU or TBTU/ DIPEA(1:2), all couplings (minimum 120 min.) were carried out in DMF. After an aqueous work up the deprotection of the Boc group was achieved with TFA. Other acid substituents were added as the HOBt or HOAt esters either by activation with HBTU/HATU, EDC or DIPCI with or without Boc protection of amino groups. The final products were purified by preparative reverse phase Hplc.

Example 20.

3-Hydroxymethylbenzoyl-D-phenylglycine-4-methylbenzylamide

Boc D-phenylglycine (251 mg, 1 mmol.) was dissolved in DMF(3ml) with HATU (380 mg., 1 mmol.) and DIPEA(350μl ., 2 mmol.). To this mixture was added 4-methylbenzylamine(121mg., 1 mmol.) and DIPEA (170μl., 1 mmol.). The mixture was stirred overnight. The mixture was then taken up into ethylacetate and washed with water, sodium carbonate solution, water, 10% hydrochloric acid solution and water. The ethylacetate was evaporated without drying and treated immediately with TFA for 30 min. The TFA was then evaporated to dryness and the product triturated with diethylether. TEA(1ml) was added and evaporated to dryness. A solution of 3-hydroxymethylbenzoic acid (76mg , 0.5mmole) in dry dimethylformamide (DMF) was treated with TBTU (161mg., 0.5mmol.) and DIPEA (1.5 mmol.). The mixture was then added to the D-phenylglycine-4-methylbenzylamide (0.5mmol.) and stirred overnight. The crude product was dissolved in water/acetonitrile (20ml), filtered and purified by preparative Hplc to yield pure product.

^{1}H nmr (CD_3CN) 7.75 (1H, m); 7.65 (2H, m); 7.30 (7H, broad m); 6.80 (3H, m); 5.40 (1H, s); 4.45 (2H,s); 4.10 (2H, m); 2.10 (3H, s). MS TOF 389 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 13.51 min.

Compounds made by the above method:-

Example 21.

3-Hydroxybenzoyl-D-phenylglycine-4-methylbenzylamide

^{1}H nmr (CD_3CN) 7.75 (1H, m); 7.40 (2H, m); 7.30 (5H, broad m); 6.95 (5H, m); 5.40 (1H, s); 4.20 (2H, m); 2.20 (3H, s). MS TOF 375 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 12.28 min.

Example 22.

3-Aminobenzoyl-D-phenylglycine-4-methylbenzylamide

^{1}H nmr (CD_3CN) 7.70-7.30 (13H, broad m); 5.65 (1H, s); 4.35 (2H, m); 2.25 (3H, s). MS TOF 374 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 10.44 min.

Example 23.

3-Amidobenzoyl-D-phenylglycine-4-methylbenzylamide

^{1}H nmr (CD_3CN) 8.40 (1H, m); 8.20 (2H, m); 7.60 (6H, broad m); 7.20 (4H, m); 5.75 (1H, s); 4.50 (2H, m); 2.40 (3H, s). MS TOF 402 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 11.16 min.

Example 24.

3-Aminomethylbenzoyl-D-phenylglycine-4-methylbenzylamide

^{1}H nmr (CD_3CN) 7.80 (2H, m); 7.45 (5H, m); 7.30 (2H, m); 6.95 (4H, m); 5.55 (1H, s); 4.25 (2H,s); 4.05 (2H, s); 2.20 (3H, s). MS TOF 388 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 12.28 min.

Example 25.

3-Amidobenzoyl-D-phenylglycine-4-(aminomethyl)benzylamide

^{1}H nmr (CD_3CN) 8.20 (1H, s); 7.95 (2H, m); 7.60 (1H,m); 7.30 (5H, broad m); 6.95 (5H, m); 5.40 (1H, s); 4.20 (2H, m); 2.20 (3H, s). MS TOF 417 ($M+1^+$). Hplc (Magellan C8, Gradient 2, water/acetonitrile/TFA) rt 14.05 min.

Example 26.

3-Aminomethylbenzoyl-D-phenylglycine-4-aminomethylcyclohexyl methylamide

^{1}H nmr (CD_3CN) 7.95 (2H, m); 7.80 (2H, m); 7.50 (5H, m); 5.65 (1H, s); 4.45 (2H, s); 3.30 (2H, m); 3.00 (2H,m); 2.00-1.00 (10H,m). MS TOF 409 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 12.68 min.

Example 27.

2-Amino-N-[1-(ethoxycarbonyl)-1-(phenyl)methyl]benzimidazole-5-carboxamide

^{1}H nmr (CD_3CN) 7.80 (1H, s); 7.55 (1H, d); 7.40 (5H, m); 7.20 (1H,d); 5.85 (1H, s); 4.15 (2H, m); 1.25 (3H, m). MS TOF 339 ($M+1^+$). Hplc (Magellan C8, Gradient 2,

water/acetonitrile/TFA) rt 17.05 min.

Example 28.

3-Aminomethylbenzoyl-D-phenylglycine-1-adamantylamide

^{1}H nmr (CD_3CN) 7.95 (1H, s); 7.85 (2H, d); 7.60 (1H, m); 7.50 (2H,m); 7.40 (3H,m); 5.65 (1H, s); 4.20 (2H, s); 2.50-1.50 (15H,m). MS TOF 418 ($M+1^+$). Hplc (Magellan C8, Gradient 1, water/acetonitrile/TFA) rt 18.36 min.

Example 29.

2-Aminobenzoyl-D-phenylglycine-N-(4-fluoro-2-methylsulphonylphenyl)piperazinamide

^{1}H nmr (DMSO) 7.65 (3H, m); 7.45 (1H, m); 7.35 (5H, m);7.15 (1H,m); 6.65 (1H,d); 6.55 (1H,m); 6.05 (1H, s); 3.15 (3H,s); 3.00-2.00 (8H,m). MS TOF 511 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 13.43 min.

Example 30.

2-Amino-4-chlorobenzoyl-D-phenylglycine-N-(4-fluoro-2-methylsulphonylphenyl)piperazinamide

^{1}H nmr (DMSO) 7.55 (3H, m); 7.45 (1H, m); 7.35 (5H, m);7.15 (1H,m); 6.75 (1H,s); 6.55 (1H,d); 6.05 (1H, s); 3.15 (3H,s); 3.00-2.00 (8H,m). MS TOF 546 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 15.18 min.

Example 31.

2-Amino-5-fluorobenzoyl-D-phenylglycine-N-(4-fluoro-2-methylsulphonylphenyl)piperazinamide

^{1}H nmr ($CDCl_3$) 7.75 (1H, m); 7.60 (1H, m); 7.25 (6H, m);7.15 (1H,m); 6.90 (1H,m); 6.75 (1H,m); 5.85 (1H, s); 3.15 (3H,s); 3.00-2.00 (8H,m). MS TOF 529 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 13.87 min.

Example 32.

2-Amino-4-methylbenzoyl-D-phenylglycine-N-(4-fluoro-2-methylsulphonylphenyl)piperazinamide

^{1}H nmr (DMSO) 7.55 (3H, m); 7.45 (2H, m); 7.35 (5H, m); 6.65 (1H,s); 6.35 (1H,d); 6.05 (1H, s); 3.15 (3H,s); 3.00-2.00 (8H,m) 2.15 (3H,s);. MS TOF 525 ($M+1^+$). Hplc

(Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 13.12 min.

Example 33.

2-Amino-5-methylbenzoyl-D-phenylglycine-N-(4-fluoro-2-methylsulphonylphenyl)piperazinamide

^{1}H nmr ($CDCl_3$) 7.75 (1H, m); 7.60 (1H, m); 7.25 (6H, m);7.15 (1H,m); 6.90 (1H,m); 6.75 (1H,m); 5.85 (1H, s); 3.15 (3H,s); 3.00-2.00 (8H,m) 2.30 (3H,s). MS TOF 525 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 12.84 min.

Example 34.

2-Amino-4-nitrobenzoyl-D-phenylglycine-N-(4-fluoro-2-methylsulphonylphenyl)piperazinamide

^{1}H nmr ($CDCl_3$) 7.75 (2H, m); 7.55 (1H, m); 7.35 (7H, m); 7.25 (1H,m); 5.80 (1H, s); 3.15 (3H,s); 3.00-2.00 (8H,m). MS TOF 556 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 15.35 min.

Example 35.

2-Amino-5-nitrobenzoyl-D-phenylglycine-N-(4-fluoro-2-methylsulphonylphenyl)piperazinamide

^{1}H nmr ($CDCl_3$) 8.25 (1H, d); 7.85 (1H, m); 7.55 (1H, m); 7.25 (7H, m); 7.05 (1H,m); 5.80 (1H, s); 3.15 (3H,s); 3.00-2.00 (8H,m). MS TOF 556 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 15.08 min.

Example 36.

2-Amino-5-cyanobenzoyl-D-phenylglycine-N-(4-fluoro-2-methylsulphonylphenyl)piperazinamide

^{1}H nmr (CD_3CN) 7.65 (4H, m); 7.25 (6H, m); 6.65 (1H,d); 5.80 (1H, s); 3.15 (3H,s); 3.00-2.00 (8H,m). MS TOF 536 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 14.89 min.

Example 37.

2,5-Diaminobenzoyl-D-phenylglycine-N-(4-fluoro-2-methylsulphonylphenyl)piperazinamide

^{1}H nmr ($CDCl_3$) 7.70 (1H, d); 7.45 (7H, m); 6.85 (1H, s); 6.55 (1H, m); 6.55 (1H,m); 5.90 (1H, s); 3.15 (3H,s); 3.00-2.00 (8H,m). MS TOF 526 ($M+1^+$). Hplc (Magellan C8,

Gradient 3, water/acetonitrile/TFA) rt 11.82 min.

Example 38.

2-Amino-4,5-dimethoxybenzoyl-D-phenylglycine-N-(4-fluoro-2-methylsulphonylphenyl)piperazinamide

^{1}H nmr (CD_3CN) 7.65 (2H, m); 7.35 (2H, m); 7.25 (5H, m); 6.75 (1H,d); 6.15 (1H, d);5.80 (1H, s); 3.60 (3H,s); 3.50 (3H,s); 3.15 (3H,s); 3.00-2.00 (8H,m). MS TOF 571 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 12.84 min.

Example 39.

Benzoyl-D-phenylglycine-N-(4-fluoro-2-methylsulphonylphenyl)piperazinamide

^{1}H nmr (CD_3CN) 7.75 (2H, m); 7.70 (1H, m); 7.40 (10H, m); 6.05 (1H, s); 3.15 (3H,s); 3.00-2.00 (8H,m). MS TOF 496 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 12.84 min.

Example 40.

2-Methylaminobenzoyl-D-phenylglycine-N-(4-fluoro-2-methylsulphonylphenyl)piperazinamide

^{1}H nmr (CD_3CN) 7.75 (1H, m); 7.65 (1H, d); 7.50 (1H, d); 7.45 (2H, m); 7.30 (5H, m); 6.80 (1H, d); 6.70 (1H, m); 6.00 (1H, s); 3.15 (3H,s); 2.80 (3H,s); 3.00-2.00 (8H,m). MS TOF 525 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 14.63 min.

Example 41.

2-Dimethylaminobenzoyl-D-phenylglycine-N-(4-fluoro-2-methylsulphonylphenyl)piperazinamide

^{1}H nmr (CD_3CN) 7.85 (1H, d); 7.50 (2H, m); 7.45 (3H, m); 7.30 (6H, m); 6.00 (1H, s); 3.15 (3H,s); 2.80 (6H,s); 3.00-2.00 (8H,m). MS TOF 539 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 12.58 min.

Example 42.

3-Aminobenzoyl-D-phenylglycine-N-(4-fluoro-2-methylsulphonylphenyl)piperazinamide

^{1}H nmr (CD_3CN) 7.85 (1H, m); 7.60 (1H, m); 7.50 (2H, m); 7.30 (7H, m); 7.05 (1H, d); 6.05 (1H, s); 3.15 (3H,s); 3.00-2.00 (8H,m). MS TOF 511 ($M+1^+$). Hplc (Magellan C8,

Gradient 3, water/acetonitrile/TFA) rt 11.32 min.

Example 43.

4-Aminobenzoyl-D-phenylglycine-N-(4-fluoro-2-methylsulphonylphenyl)piperazinamide

^{1}H nmr ($CDCl_3$) 7.95 (1H, d); 7.80-7.45 (10H, broad m); 7.35 (1H,d); 6.20 (1H, s); 3.15 (3H,s); 3.00-2.00 (8H,m). MS TOF 511 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 12.05 min.

Example 44.

3,4 Diaminobenzoyl-D-phenylglycine-N-(4-fluoro-2-methylsulphonylphenyl)piperazinamide

^{1}H nmr ($CDCl_3$) 7.75 (1H, d); 7.40-7.15 (9H, broad m); 6.55 (1H,d); 6.00 (1H, s); 3.15 (3H,s); 3.00-2.00 (8H,m). MS TOF 540 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 11.30 min.

Example 45.

3-Chlorobenzoyl-D-phenylglycine-N-(4-fluoro-2-methylsulphonylphenyl)piperazinamide

^{1}H nmr (CD_3CN) 7.85 (1H, m); 7.80 (1H, s); 7.60 (2H, m); 7.30 (8H, m); 6.00 (1H, s); 3.20 (3H,s); 3.00-2.00 (8H,m). MS TOF 531 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 15.40 min.

Example 46.

4-Chlorobenzoyl-D-phenylglycine-N-(4-fluoro-2-methylsulphonylphenyl)piperazinamide

^{1}H nmr (CD_3CN) 7.95 (1H, m); 7.75 (2H, m); 7.60 (1H, m); 7.40 (8H, m); 6.05 (1H, s); 3.25 (3H,s); 3.00-2.00 (8H,m). MS TOF 531 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 16.54 min.

Example 47.

3-Amino-4-chlorobenzoyl-D-phenylglycine-N-(4-fluoro-2-methylsulphonylphenyl)piperazinamide

^{1}H nmr ($CDCl_3$) 8.05 (1H, m); 7.80 (1H, m); 7.70 (1H, s); 7.20-7.60 (8H, broad m); 6.05 (1H, s); 3.25 (3H,s); 3.00-2.00 (8H,m). MS TOF 546 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 14.53 min.

Example 48.

4-Bromobenzoyl-D-phenylglycin -N-(4-fluoro-2-methylsulphonylphenyl)piperazinamide

^{1}H nmr (CD_3CN) 7.85 (1H, m); 7.65 (2H, m); 7.60 (2H, d); 7.45 (2H, d); 7.30 (5H, m); 6.00 (1H, s); 3.20 (3H,s); 3.00-2.00 (8H,m). MS TOF 576 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 15.94 min.

Example 49.

4-Iodobenzoyl-D-phenylglycine-N-(4-fluoro-2-methylsulphonylphenyl)piperazinamide

^{1}H nmr (CD_3CN)); 7.75 (2H, m); 7.65 (1H, m 7.55 (2H, d); 7.45 (2H, d); 7.30 (5H, m); 5.95 (1H, s); 3.20 (3H,s); 3.00-2.00 (8H,m). MS TOF 622 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 15.96 min.

Example 50.

3-Amino-4-methylbenzoyl-D-phenylglycine-N-(4-fluoro-2-methylsulphonylphenyl)piperazinamide

^{1}H nmr ($CDCl_3$) 7.95 (1H, s); 7.60 (1H, d); 7.45 (1H, d); 7.40-7.15 (8H, broad m); 6.00 (1H, s); 3.15 (3H,s); 3.00-2.50 (8H,m) 2.20 (3H, s). MS TOF 525 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 11.71 min.

Example 51.

4-Methoxybenzoyl-D-phenylglycine-N-(4-fluoro-2-methylsulphonylphenyl)piperazinamide

^{1}H nmr (CD_3CN) 7.85 (2H, d); 7.65 (1H, m); 7.50 (2H, m); 7.40 (5H, m); 6.80 (2H, d); 6.00 (1H, s); 3.80 (3H, s); 3.20 (3H,s); 3.00-2.00 (8H,m). MS TOF 526 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 14.63 min.

Example 52.

3-Amino-4-methoxybenzoyl-D-phenylglycine-N-(4-fluoro-2-methylsulphonylphenyl)piperazinamide

^{1}H nmr ($CDCl_3$) 7.90 (1H, m); 7.75 (1H, d); 7.60 (2H, m); 7.40-7.15 (6H, broad m); 7.45 (1H, d); 6.10 (1H, s); 3.95 (3H, s); 3.35 (3H,s); 3.00-2.50 (8H,m). MS TOF 541 ($M+1^+$). Hplc (Magellan C8, Gradient 3,

water/acetonitrile/TFA) rt 11.78 min.

Example 53.

3,4-Dihydroxybenzoyl-D-phenylglycine-N-(4-fluoro-2-methylsulphonylphenyl)piperazinamide

^{1}H nmr ($CDCl_3$) 7.55 (1H, m); 7.45 (1H, d); 7.25 (2H, m); 7.15 (5H, m); 7.00 (1H, d); 6.60 (1H, d); 5.80 (1H, s); 3.05 (3H, s); 3.00-2.50 (8H, m). MS TOF 541 (M+1$^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 11.78 min.

Example 54.

Naphth-2-oyl-D-phenylglycine-N-(4-fluoro-2-methylsulphonylphenyl)piperazinamide

^{1}H nmr ($CDCl_3$) 8.35 (1H, s); 8.00 (1H, d); 7.85 (5H, m); 7.45 (4H, m); 7.25 (4H, m); 6.10 (1H, s); 3.20 (3H,s); 3.00-2.50 (8H,m). MS TOF 546 (M+1$^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 16.66 min.

Example 55.

3-Aminonaphth-2-oyl-D-phenylglycine-N-(4-fluoro-2-methylsulphonylphenyl)piperazinamide

^{1}H nmr ($CDCl_3$) 8.15 (1H, d); 8.00 (1H, s); 7.75 (2H, m); 7.65 (1H, d); 7.30 7.60 (9H, m); 6.10 (1H, s); 3.25 (3H,s); 3.00-2.50 (8H,m). MS TOF 561 (M+1$^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 13.90 min.

Example 56.

Thiophene-3-oyl-D-phenylglycine-N-(4-fluoro-2-methylsulphonylphenyl)piperazinamide

^{1}H nmr ($CDCl_3$) 8.15 (1H, s); 7.95 (1H, m); 7.85 (1H, m); 7.60 (8H, m); 6.30 (1H, s); 3.45 (3H,s); 2.00-2.50 (8H,m). MS TOF 502 (M+1$^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 14.28 min.

Example 57.

Thiophene-2-oyl-D-phenylglycine-N-(4-fluoro-2-methylsulphonylphenyl)piperazinamide

^{1}H nmr ($CDCl_3$) 7.65 (2H, m); 7.45 (1H, s); 7.30 (2H, m); 7.20 (5H, m); 6.95 (1H, m); 6.00 (1H, s); 3.05 (3H,s); 3.00-2.50 (8H,m). MS TOF 502 (M+1$^+$). Hplc (Magellan C8,

Gradient 3, water/acetonitrile/TFA) rt 14.52 min.

Example 58.

5-Methyl thiophene-2-oyl-D-phenylglycine-N-(4-fluoro-2-methylsulphonylphenyl)piperazinamide

^{1}H nmr ($CDCl_3$) 7.70 (1H, m); 7.45 (2H, m); 7.35 (6H, m); 6.65 (1H, m); 6.00 (1H, s); 3.05 (3H,s); 3.00-2.50 (8H,m) 2.45 (3H, s). MS TOF 516 (M+1$^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 14.98 min.

Example 59.

Isoquinolin-7-oyl-D-phenylglycine-N-(4-fluoro-2-methylsulphonylphenyl)piperazinamide

^{1}H nmr (CD_3CN) 9.50 (1H, s); 8.75 (1H, s); 8.55 (1H, d); 8.30 (1H, d); 8.10 (2H, m); 7.65 (1H, m); 7.45 (2H, m); 7.35 (5H, m); 6.10 (1H, s); 3.20 (3H,s); 3.00-2.50 (8H,m). MS TOF 547 (M+1$^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 11.39 min.

Example 60.

Pyridin-3-oyl-D-phenylglycine-N-(4-fluoro-2-methylsulphonylphenyl)piperazinamide

^{1}H nmr (CD_3CN) 9.00 (1H, s); 8.70 (1H, d); 8.35 (1H, d); 8.10 (1H, m); 7.65 (2H, m); 7.45 (1H, m); 7.30 (5H, m); 6.00 (1H, s); 3.20 (3H,s); 3.00-2.50 (8H,m). MS TOF 497 (M+1$^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 11.99 min.

Example 61.

Indol-6-oyl-D-phenylglycine-N-(4-fluoro-2-methylsulphonylphenyl)piperazinamide

^{1}H nmr (CD_3CN) 7.95 (2H, m); 7.60 (2H, m); 7.50 (3H, m); 7.35 (5H, m);6.45 (1H, s); 6.05 (1H, s); 3.25 (3H,s); 3.00-2.50 (8H,m). MS TOF 535 (M+1$^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 15.44 min.

Example 62.

2,4-Diaminobenzoyl-D-phenylglycine-N-(4-fluoro-2-methylsulphonylphenyl)piperazinamide

MS TOF 526 (M+1$^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 11.89 min.

Example 63.

4-Methylaminobenzoyl-D-phenylglycine-N-(4-fluoro-2-methyl sulphonylphenyl)piperazinamide

^{1}H nmr (CD_3CN) 7.65 (3H, m); 7.50 (2H, m); 7.35 (5H, m); 6.60 (2H, d); 6.05 (1H, s); 3.30 (3H, s); 3.00-2.50 (8H, m); 2.80 (3H, s). MS TOF 525 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 13.17 min.

Example 64.

3-Methyl-4-chlorobenzoyl-D-phenylglycine-N-(4-fluoro-2-methyl sulphonylphenyl)piperazinamide

^{1}H nmr (CD_3CN) 7.90 (1H, s); 7.85 (1H, s); 7.80 (1H, s); 7.55 (6H, m); 6.25 (1H, s); 3.45 (3H, s); 3.00-2.50 (8H, m); 2.60 (3H, s). MS TOF 545 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 16.39 min.

Example 65.

4-Vinylbenzoyl-D-phenylglycine-N-(4-fluoro-2-methyl sulphonylphenyl)piperazinamide

^{1}H nmr (CD_3CN) 7.75 (2H, d); 7.60 (1H, m); 7.45 (4H, m); 7.35 (5H, m); 6.75 (1H, m); 6.05 (1H, s); 5.90 (1H, d); 5.30 (1H, d); 3.00-2.50 (8H, m); 2.80 (3H, s). MS TOF 522 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 15.45 min.

Example 66.

3-Amino-4-hydroxybenzoyl-D-phenylglycine-N-(4-fluoro-2-methyl sulphonylphenyl)piperazinamide

^{1}H nmr (CD_3CN) 7.60 (1H, m); 7.50-7.10 (9H, m); 7.35 (1H, d); 5.95 (1H, s); 3.25 (3H, s); 3.00-2.50 (8H, m). MS TOF 527 ($M+1^+$). Hplc (Magellan C8, Gradient 2, water/acetonitrile/TFA) rt 15.46 min.

Example 67.

4-Methylthiobenzoyl-D-phenylglycine-N-(4-fluoro-2-methyl sulphonylphenyl)piperazinamide

^{1}H nmr (CD_3CN) 7.85 (2H, d); 7.80 (1H, m); 7.60 (2H, m); 7.50 (5H, m); 7.40 (2H, d); 6.15 (1H, s); 3.40 (3H, s); 3.10-2.70 (8H, m); 2.60 (3H, s). MS TOF 542 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 16.67 min.

Example 68.

3 Carboxamidobenzoyl-D-phenylglycine-N-(4-fluoro-2-methyl sulphonylphenyl)piperazinamide

^{1}H nmr (CD_3CN) 8.25 (1H, s); 7.95 (2H, d); 7.70 (1H, m); 7.55 (3H, m); 7.40 (5H, m); 6.05 (1H, s); 3.30 (3H, s); 3.00-2.50 (8H, m). MS TOF 539 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 12.83 min.

Example 69.

3-Amino-4-methylcarboxybenzoyl-D-phenylglycine-N-(4-fluoro-2-methyl sulphonylphenyl)piperazinamide

^{1}H nmr (CD_3CN) 7.90 (1H, d);7.70 (1H, m); 7.55 (2H, m); 7.45 (5H, m); 7.20 (1H, s); 6.95 (1H, d); 6.05 (1H, s); 3.80 (3H, s); 3.30 (3H, s); 3.00-2.50 (8H, m). MS TOF 569 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 14.49 min.

Example 70.

3-Methyl-4-bromobenzoyl-D-phenylglycine-N-(4-fluoro-2-methyl sulphonylphenyl)piperazinamide

^{1}H nmr (CD_3CN) 7.65 (3H, m); 7.45 (3H, m); 7.30 (5H, m); 6.00 (1H, s); 3.25 (3H, s); 3.00-2.50 (8H, m); 2.40 (3H, s). MS TOF 589 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 16.67 min.

Example 71.

4-Ethoxybenzoyl-D-phenylglycine-N-(4-fluoro-2-methyl sulphonylphenyl)piperazinamide

^{1}H nmr (CD_3CN) 7.75 (2H, d); 7.60 (1H, m); 7.50 (2H, m); 7.35 (5H, m); 6.85 (2H, d); 6.00 (1H, s); 4.00 (2H, m); 3.20 (3H, s); 3.00-2.50 (8H, m); 1.30 (3H, t). MS TOF 540 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 16.58 min.

Example 72.

5-Indoloyl-D-phenylglycine-N-(4-fluoro-2-methyl sulphonylphenyl)piperazinamide

^{1}H nmr (CD_3CN) 8.15 (1H, s); 7.95 (1H, m); 7.65 (2H, m); 7.60-7.35 (7H, m); 6.60 (1H, s); 6.10 (1H, s); 3.30 (3H, s); 3.00-2.60 (8H, m). MS TOF 535 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 13.88 min.

Example 73.

5 Benzamidazoyl-D-phenylglycine-N-(4-fluoro-2-methyl sulphonylphenyl)piperazinamide

^{1}H nmr (CD_3CN) 8.75 (1H, s); 8.25 (1H, s); 7.75 (2H, m); 7.60 (1H, m); 7.50 (2H, m); 7.35 (5H, m); 6.60 (2H, d); 6.05 (1H, s); 3.30 (3H, s); 3.00-2.50 (8H, m). MS TOF 536 (M+1$^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 10.08 min.

Example 74.

3-Aminobenzoyl-D-phenylglycine-1'-methyl-4,4'bispiperidinamide

^{1}H nmr (CD_3CN) a mixture of conformers only one recorded here 7.65 (1H, m); 7.35 (5H, m); 7.05 (1H, m); 6.95 (2H, m); 5.85 (1H, s); 4.45 (1H, m); 3.85 (1H, m); 3.30 (2H, m); 2.90-2.40 (8H, m); 2.55 (3H, s); 1.60 (2H, m); 1.30 (2H, m); 1.00 (2H, m). MS TOF 435 (M+1$^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 7.65 min.

Example 75.

3-Amino-4-chlorobenzoyl-D-phenylglycine-1'-methyl-4,4'bispiperidinamide

^{1}H nmr (CD_3CN) a mixture of conformers only one recorded here 7.75 (1H, m); 7.30 (5H, m); 7.20 (1H, m); 6.95 (1H, m); 5.85 (1H, s); 4.45 (1H, m); 3.85 (1H, m); 3.30 (2H, m); 2.90-2.40 (8H, m); 2.55 (3H, s); 1.60 (2H, m); 1.30 (2H, m); 1.00 (2H, m). MS TOF 469 (M+1$^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 9.58 min.

Example 76.

3-Amino-4-methylbenzoyl-D-phenylglycine-1'-methyl-4,4'bispiperidinamide

^{1}H nmr (CD_3CN) a mixture of conformers only one recorded here 7.75 (1H, m); 7.35 (5H, m); 7.05 (2H, m); 5.85 (1H, s); 4.45 (1H, m); 3.85 (1H, m); 3.30 (2H, m); 2.90-2.40 (8H, m); 2.65 (3H, s); 2.15 (3H, s); 1.60 (2H, m); 1.30 (2H, m); 1.00 (2H, m). MS TOF 449 (M+1$^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt

8.03 min

Example 77.

3-Aminonaphth-2-oyl-D-phenylglycine-1'-methyl-4,4'bispiperidinamide

^{1}H nmr (CD_3CN) a mixture of conformers only one recorded here 7.95 (1H, m); 7.65 (1H, d); 7.45 (2H, m); 7.30 (5H, m); 7.15 (1H, m); 6.95 (1H, s) 5.95 (1H, s); 4.45 (1H, m); 3.85 (1H, m); 3.30 (2H, m); 2.90-2.40 (8H, m); 2.65 (3H, s); 1.60 (2H, m); 1.30 (2H, m); 1.00 (2H, m). MS TOF 485 ($M+1^+$). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 9.94 min.

Example 78.

Indol-6-oyl-D-phenylglycine-1'-methyl-4,4'-bispiperidinamide

^{1}H nmr (CD_3CN) a mixture of conformers only one recorded here7.78 (2H, s); 7.50 (1H, d); 7.25(7H, m); 6.34 (1H, s); 6.82 (1H, s); 4.40 (1H, m); 3.83 (1H, m); 3.35 (2H, t); 2.9-2.4 (8H, m) and 2.65 (3H, s) masked by water in solvent; 1.60 (2H, m); 1.40 (2H, m); 1.08 (2H, m). MS TOF 459 ($M+1^+$).

Hplc (Luna2 C18, Gradient 3, water/acetonitrile/TFA rt 10.01 min.

Example 79.

3-Amino-4-fluorobenzoyl-D-phenylglycine-1'-methyl-4,4'-bispiperidinamide

^{1}H nmr (d_4 methanol) a mixture of conformers only one recorded here 7.4 (6H, m); 7.1 (1H, m); 7.0 (1H, t); 6.0 (1H, s); 4.63 (1H, m); 4.02 (1H, m); 3.30 (2H, m); 2.90-2.40 (8H, m); 2.65 (3H, s); 1.60 (2H, m); 1.30 (2H, m); 1.00 (2H, m). MS TOF 453 ($M+1^+$).

Hplc (Symmetry C8, Gradient 3, water/acetonitrile/TFA) rt 5.03 min.

Example 80.

3-Amino-4-bromobenzoyl-D-phenylglycine-1'-methyl-4,4'-bispiperidinamide

^{1}H nmr (CD_3CN) a mixture of conformers only one recorded here 7.75 (1H, m); 7.35 (5H, m); 7.05 (1H, m); 6.80

(1H, m); 5.85 (1H, s); 4.45 (1H, m); 3.85 (1H, m); 3.30 (2H, m); 2.90-2.40 (8H, m) and 2.65 (3H, s) masked by water in solvent; 1.60 (2H, m); 1.30 (2H, m); 1.00 (2H, m). MS TOF 513 and 515 $(M+1^+)$.
(Symmetry C8, Gradient 3, water/acetonitrile/TFA) rt 5.70 min.

Example 81.

3-Amino-4-methoxybenzoyl-D-phenylglycine-1'-methyl-4,4'-bispiperidinamide

^1H nmr (CD_3CN) a mixture of conformers only one recorded here 7.70 (1H, m); 7.30 (5H, m); 7.0 (2H, m); 6.72 (1H, d); 5.80 (1H, s); 4.45 (1H, m); 3.85(1H, m); 3.70(3H, s); 3.30 (2H, m); 2.9-2.4 (8H, m) masked by water in solvent; 1.60 (2H, m); 1.30 (2H, m); 1.00 (2H, m). MS TOF 465 $(M+1^+)$.
Hplc (Luna2 C18, Gradient 3, water/acetonitrile/TFA) rt 7.55 min.

Example 82.

4-(Methylamino)benzoyl-D-phenylglycine-1'-methyl-4,4'-bispiperidinamide

^1H nmr (CD_3CN) a mixture of conformers only one recorded here 7.70 (3H, m); 7.35 (5H, m); 6.60 (2H, d); 5.90 (1H, s); 4.45 (1H, m); 3.85(1H, m); 3.40 (2H, m); 2.9-2.4 (8H, m);2.70 (3H, s); 1.60 (2H, m); 1.30 (2H, m); 1.00 (2H, m). MS TOF 465 $(M+1^+)$.
Hplc (Luna2 C18, Gradient 3, water/acetonitrile/TFA) rt 8.52 min.

Example 83.

4-Ethylaminobenzoyl-D-phenylglycine-N-(4-fluoro-2-methyl sulphonylphenyl)piperazinamide

1H nmr (CD3CN) 7.65 (3H, m); 7.45 (2H, m); 7.35 (5H, m); 6.60 (2H, d); 6.00 (1H, s); 3.20 (3H, s); 3.10 (2H, q); 3.00-2.50 (8H, m); 1.15 (3H, t). MS TOF 539 (M+1+).
Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 12.57 min.

Example 84.

3-Methylaminobenzoyl-D-phenylglycine-N-(4-fluoro-2-methyl sulphonylphenyl)piperazinamide

1H nmr (CD3CN) 7.75 (1H, d); 7.60 (1H, d); 7.35 (7H, m); 7.15 (1H, t); 7.00 (1H, m); 6.70 (1H, d); 6.00 (1H, s); 3.20 (3H, s); 3.00-2.50 (8H, m); 2.70 (3H, s). MS TOF 525 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 12.07 min.

Example 85.

4-Chloro-3-aminobenzoyl-D-phenylglycine-N-2-methyl sulphonylphenyl piperazinamide

1H nmr (CD3CN) 7.95 (1H, d); 7.60 (1H, m); 7.45 (10H, m); 7.00 (1H, d); 6.00 (1H, s); 3.25 (3H, s); 3.00-2.50 (8H, m). MS TOF 527 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 13.56 min.

Example 86.

4-Trifluoromethoxybenzoyl-D-phenylglycine-N-(4-fluoro-2-methyl sulphonylphenyl)piperazinamide

1H nmr (CD3CN) 7.85 (3H, m); 7.65 (1H, d); 7.45 (2H, m); 7.35 (6H, m); 6.00 (1H, s); 3.25 (3H, s); 3.00-2.50 (8H, m). MS TOF 580 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 16.01 min.

Example 87.

4-Difluoromethoxybenzoyl-D-phenylglycine-N-(4-fluoro-2-methyl sulphonylphenyl)piperazinamide

1H nmr (CD3CN) 7.85 (3H, m); 7.45 (2H, d); 7.30 (5H, m); 7.15 (2H, d); 6.80 (1H, t); 6.00 (1H, s); 3.20 (3H, s); 3.00-2.50 (8H, m). MS TOF 562 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 14.99 min.

Example 88.

4-Trifluoromethylbenzoyl-D-phenylglycine-N-(4-fluoro-2-methyl sulphonylphenyl)piperazinamide

1H nmr (CD3CN) 7.85 (2H, d); 7.70 (2H, d); 7.45 (2H, m); 7.35 (6H, m); 6.00 (1H, s); 3.20 (3H, s); 3.00-2.50 (8H, m). MS TOF 564 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 15.00 min.

Example 89.
Indol-3-oyl-D-phenylglycine-N-(4-fluoro-2-methyl sulphonylphenyl)piperazinamide
1H nmr (CD3CN) 8.05 (1H,s); 7.85 (1H, d); 7.70 (1H, m);7.50 (2H, m); 7.35 (6H, m); 7.20 (2H, m); 6.15 (1H, s); 3.20 (3H, s); 3.00-2.50 (8H, m). MS TOF 535 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 14.25 min.

Example 90.
4-Chloro-3-aminobenzoyl-L-phenylglycine-N-(4-fluoro-2-methyl sulphonylphenyl)piperazinamide
1H nmr (CD3CN) 7.75 (1H, d); 7.60 (1H, d); 7.45 (8H, m); 6.90 (1H, d); 5.95 (1H, s); 3.20 (3H, s); 3.00-2.50 (8H, m). MS TOF 545 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 14.53 min.

Example 91.
2-Carboxylbenzoyl-D-phenylglycine-N-(4-fluoro-2-methyl sulphonylphenyl)piperazinamide
1H nmr (CD3CN) 7.75 (1H, d); 7.60 (1H, d); 7.50 (1H, d); 7.25-7.50 (9H, m); 6.00 (1H, s); 3.20 (3H, s); 3.00-2.50 (8H, m). MS TOF 540 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 12.19 min.

Example 92.
2-Carboxamidobenzoyl-D-phenylglycine-N-(4-fluoro-2-methyl sulphonylphenyl)piperazinamide
1H nmr (CD3CN) 7.75 (1H, d); 7.60 (1H, d); 7.25-7.50 (10H, m); 6.00 (1H, s); 3.20 (3H, s); 3.00-2.50 (8H, m). MS TOF 539 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 12.29 min.

Example 93.

2-Fluorobenzoyl-D-phenylglycine-N-(4-fluoro-2-methyl sulphonylphenyl)piperazinamide

1H nmr (CD3CN) 7.85 (1H, m); 7.60 (1H, d); 7.25-7.50 (10H, m); 6.00 (1H, s); 3.20 (3H, s); 3.00-2.50 (8H, m). MS TOF 514 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 13.29 min.

Example 94.

3-Bromo indol-6-oyl-D-phenylglycine-N-(4-fluoro-2-methyl sulphonylphenyl)piperazinamide

1H nmr (CD3CN) 7.85 (2H, m); 7.70-7.20 (10H, m); 6.05 (1H, s); 3.20 (3H, s); 3.00-2.50 (8H, m). MS TOF 614 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 16.16 min.

Example 95.

3-Chloro indol-6-oyl-D-phenylglycine-N-(4-fluoro-2-methyl sulphonylphenyl)piperazinamide

1H nmr (CD3CN) 7.95 (2H, m); 7.70-7.30 (10H, m); 6.05 (1H, s); 3.25 (3H, s); 3.00-2.50 (8H, m). MS TOF 570 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 16.18 min.

Example 96.

2-Cyanobenzoyl-D-phenylglycine-N-(4-fluoro-2-methyl sulphonylphenyl)piperazinamide

1H nmr (CD3CN) 7.25-7.80 (12H, m); 6.05 (1H, s); 3.25 (3H, s); 3.00-2.50 (8H, m). MS TOF 521 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 14.85 min.

Example 97.

2-Aminomethylbenzoyl-D-phenylglycine-N-(4-fluoro-2-methy l sulphonylphenyl)piperazinamide

1H nmr (CD3CN) 7.95 (2H, m); 7.80-7.35 (10H, m); 6.15

(1H, s); 4.30 (2H, s); 3.15 (3H, s); 3.00-2.50 (8H, m). MS TOF 525 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 12.21 min.

Example 98.

4-Carboxyl-3-aminobenzoyl-D-phenylglycine-N-(4-fluoro-2-methyl sulphonylphenyl)piperazinamide

1H nmr (CD3CN) 7.75 (1H, d); 7.60 (1H, d); 7.45 (7H, m); 7.15 (1H, s);6.85 (1H,d); 5.95 (1H, s); 3.25 (3H, s); 3.00-2.50 (8H, m). MS TOF 554 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 13.00 min.

Example 99.

1H-Indazol-6-oyl-D-phenylglycine-N-(4-fluoro-2-methyl sulphonylphenyl)piperazinamide

1H nmr (CD3CN) 8.05 (2H,m); 7.85 (1H, d); 7.70 (1H, d); 7.55 (2H, m); 7.45 (5H, m); 5.95 (1H, s); 3.30 (3H, s); 3.00-2.50 (8H, m). MS TOF 545 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 13.44 min.

Example 100.

4-Methylcarboxylbenzoyl-D-phenylglycine-N-(4-fluoro-2-methyl sulphonylphenyl)piperazinamide

1H nmr (CD3CN) 7.95 (2H, m); 7.80 (2H, m); 7.45 (2H, m); 7.35 (6H, m); 6.00 (1H, s); 3.90 (3H, s); 3.20 (3H, s); 3.00-2.50 (8H, m). MS TOF 554 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 14.90 min.

Example 101.

4-Acetoxybenzoyl-D-phenylglycine-N-(4-fluoro-2-methyl sulphonylphenyl)piperazinamide

1H nmr (CD3CN) 7.75 (3H, m); 7.60 (1H, d); 7.45 (2H, m); 7.35 (5H, m); 7.10 (2H,d); 6.00 (1H, s); 3.20 (3H, s); 3.00-2.50 (8H, m); 2.20 (3H,s).MS TOF 554 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA)

rt 14.53 min.

Example 102.

5-Methylpyrazin-2-oyl-D-phenylglycine-N-(4-fluoro-2-methyl sulphonylphenyl)piperazinamide

1H nmr (CD3CN) 8.90 (1H,s); 8.35 (1H,s); 7.55 (1H, m); 7.40 (2H, m); 7.25 (5H, m); 5.85 (1H, s); 3.10 (3H, s); 3.00-2.50 (8H, m); 2.40 (3H, s). MS TOF 512 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 14.17 min.

Example 103.

1,3 Benzodioxol-5-oyl-D-phenylglycine-N-(4-fluoro-2-methyl sulphonylphenyl)piperazinamide

1H nmr (CD3CN) 7.55 (2H, m); 7.35 (2H, m); 7.25 (6H, m); 6.70 (1H,d); 5.85 (2H,s); 5.80 (1H, s); 3.10 (3H, s); 3.00-2.50 (8H, m). MS TOF 540 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 14.28 min.

Example 104.

4-(Methylsulphonyl)benzoyl-D-phenylglycine-N-(4-fluoro-2-methyl sulphonylphenyl)piperazinamide

1H nmr (CD3CN) 7.95 (3H, m); 7.60 (1H, m); 7.50 (2H,m); 7.35 (6H, m); 6.05 (1H, s); 3.25 (3H,s); 3.10 (3H, s); 3.00-2.50 (8H, m). MS TOF 574 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 13.62 min.

Example 105.

2,3 Dichloroindol-6-oyl-D-phenylglycine-N-(4-fluoro-2-methyl sulphonylphenyl)piperazinamide

1H nmr (CD3CN) 7.90 (1H,d); 7.85 (1H,s); 7.55 (2H, m); 7.40 (2H, m); 7.25 (5H, m); 6.05 (1H, s); 3.30 (3H, s); 3.00-2.50 (8H, m); 2.40 (3H, s). MS TOF 614 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA)

rt 16.35 min.

Example 106.

3-Chloro-2-oxo-(1H)indol-6-oyl-D-phenylglycine-N-(4-fluoro-2-methyl sulphonylphenyl)piperazinamide

1H nmr (CD3CN) 7.90 (1H,d); 7.55 (1H, m); 7.25-7.50 (9H, m); 5.95 (1H, s); 5.20 (1H,s); 3.20 (3H, s); 3.00-2.50 (8H, m). MS TOF 585 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 14.38 min.

Example 107.

3,3-Dichloro-2-oxo-(1H)indol-6-oyl-D-phenylglycine-N-(4-fluoro-2-methyl sulphonylphenyl)piperazinamide

1H nmr (CD3CN) 7.90 (1H,d); 7.65 (2H,m); 7.55 (1H, m); 7.45 (2H,m); 7.35 (5H, m); 5.95 (1H, s); 3.25 (3H, s); 3.00-2.50 (8H, m). MS TOF 619 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 15.13 min.

Example 108.

3-Methylindol-6-oyl-D-phenylglycine-1'-methyl-4,4'bispiperidinamide

1H nmr (CD3CN) a mixture of conformers only one recorded here 7.85 (2H, m); 7.40 (3H, m); 7.30 (3H, m); 7.05 (1H, s); 5.95 (1H, s); 4.55 (1H, m); 3.85 (1H, m); 3.30 (2H, m); 2.90-2.40 (8H, m); 2.55 (3H, s); 2.20 (3H,s); 1.60 (2H, m); 1.30 (2H, m); 1.00 (2H, m). MS TOF 473 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 12.40 min.

Example 109.

2,3-Dihydroindol-6-oyl-D-phenylglycine-1'-methyl-4,4'-bispiperidinamide

1H nmr (CD3CN) a mixture of conformers only one recorded here 7.75 (1H, m); 7.30 (7H, m); 5.85 (1H, s); 4.45 (1H, m); 3.85 (1H, m); 3.65 (2H,t);3.30 (2H, m); 3.10 (2H,t); 2.90-2.40 (8H, m); 2.55 (3H, s); 1.60 (2H, m); 1.30 (2H, m); 1.00 (2H, m). MS TOF 461 (M+1+). Hplc

(Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 8.68 min.

Example 110.

Azaindol-6-oyl-D-phenylglycine-1'-methyl-4,4'bispiperidinamide

1H nmr (CD3CN) a mixture of conformers only one recorded here 7.95 (1H, m); 7.85 (2H,m); 7.65 (1H,m); 7.45 (2H, m); 7.30 (3H, m); 5.95 (1H, s); 4.55 (1H, m); 3.95 (1H, m); 3.30 (2H, m); 2.90-2.40 (8H, m); 2.55 (3H, s); 1.60 (2H, m); 1.30 (2H, m); 1.00 (2H, m). MS TOF 460 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 9.72 min.

Example 111.

Benzimidazol-5-oyl-D-phenylglycine-1'-methyl-4,4'-bispiperidinamide

1H nmr (CD3CN) a mixture of conformers only one recorded here. 8.05 (1H,s); 7.90 (1H,m); 7.75 (2H, m); 7.30 (5H, m); 5.95 (1H, s); 4.45 (1H, m); 3.85 (1H, m); 3.30 (2H, m); 2.90-2.40 (8H, m); 2.75 (3H, s); 1.60 (2H, m); 1.30 (2H, m); 1.00 (2H, m). MS TOF 460 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 8.80 min.

Example 112.

Benzthiazol-6-oyl-D-phenylglycine-1'-methyl-4,4'-bispiperidinamide

1H nmr (CD3CN) a mixture of conformers only one recorded here 8.40 (1H,s); 7.95 (3H, m); 7.30 (5H, m); 5.85 (1H, s); 4.45 (1H, m); 3.85 (1H, m); 3.30 (2H, m); 2.90-2.40 (8H, m); 2.65 (3H, s); 1.60 (2H, m); 1.30 (2H, m); 1.00 (2H, m). MS TOF 477 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 9.58 min.

Example 113.

3-Chloroindol-6-oyl-D-phenylglycine-1'-methyl-4,4'-

bispiperidinamide

1H nmr (CD3CN) a mixture of conformers only one recorded here 7.85 (2H, m); 7.30 (7H, m); 5.85 (1H, s); 4.45 (1H, m); 3.85 (1H, m); 3.30 (2H, m); 2.90-2.40 (8H, m); 2.65 (3H, s); 1.60 (2H, m); 1.30 (2H, m); 1.00 (2H, m). MS TOF 493 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 12.22 min.

Example 114.

3-Bromoindol-6-oyl-D-phenylglycine-1'-methyl-4,4'-bispiperidinamide

1H nmr (CD3CN) a mixture of conformers only one recorded here 7.85 (2H, m); 7.30 (7H, m); 5.85 (1H, s); 4.45 (1H, m); 3.85 (1H, m); 3.30 (2H, m); 2.90-2.40 (8H, m); 2.65 (3H, s); 1.60 (2H, m); 1.30 (2H, m); 1.00 (2H, m). MS TOF 539 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 12.45min.

Example 115.

3-Amino-4-chlorobenzoyl-L-phenylglycine-1'-methyl-4,4'-bispiperidinamide

1H nmr (CDCl3) a mixture of conformers only one recorded here 7.65 (1H, m); 7.30 (6H, m); 7.00 (1H,m); 5.85 (1H, s); 4.65 (1H, m); 3.80 (1H, m); 3.55 (2H, m); 2.90-2.40 (8H, m); 2.65 (3H, s); 1.60 (2H, m); 1.30 (2H, m); 1.00 (2H, m). MS TOF 469 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 10.71min.

Example 116.

4-Vinylbenzoyl-D-phenylglycine-1'-methyl-4,4'bispiperidinamide

1H nmr (CD3CN) a mixture of conformers only one recorded here 7.85 (1H, m); 7.70 (2H,m); 7.40 (6H, m); 6.75 (1H,m); 6.00 (1H, s); 5.85 (1H,d); 5.50 (1H,d); 4.55 (1H, m); 3.95 (1H, m); 3.30 (2H, m); 2.90-2.40 (8H, m); 2.65 (3H, s); 1.60 (2H, m); 1.30 (2H, m); 1.00 (2H, m). MS TOF 446 (M+1+). Hplc (Magellan C8, Gradient 3,

water/acetonitrile/TFA) rt 11.21min.

Example 117.

3-Amino-4-chlorobenzoyl-D-phenylglycine-N-(4-amino-2-methyl sulphonylphenyl)piperazinamide

1H nmr (CD3CN) 7.55 (1H, m); 7.45 (3H, m); 7.35 (5H, m); 7.10 (1H,d); 6.90 (1H, d); 6.10 (1H, s); 3.20 (3H, s); 3.00-2.50 (8H, m). MS TOF 542 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 12.02 min.

Example 118.

3-Aminobenzoyl-D-phenylglycine-N-(4-amino-2-methyl sulphonylphenyl)piperazinamide

1H nmr (CD3CN) 7.55 (2H, m); 7.45 (3H, m); 7.35 (5H, m); 7.10 (1H,d); 6.90 (1H, d); 6.10 (1H, s); 3.10 (3H, s); 3.00-2.50 (8H, m). MS TOF 508 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 9.35 min.

Example 119.

3-Amino-4-chlorobenzoyl-D-phenylglycine-N-(4-carboxamido-2-methyl sulphonylphenyl)piperazinamide

1H nmr (CD3CN) 8.05 (1H,d); 7.80 (1H, m); 7.35-7.60 (8H, m); 7.10 (1H,d); 6.10 (1H, s); 3.25 (3H, s); 3.00-2.50 (8H, m). MS TOF 570 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 12.24 min.

Example 120.

3-Amino-4-chlorobenzoyl-D-phenylglycine-N-(4-nitro-2-methyl sulphonylphenyl)piperazinamide

1H nmr (CD3CN) 8.70 (1H.s); 8.45 (1H,d); 7.55 (1H, m); 7.45 (5H, m); 7.30 (2H, m); 7.10 (1H,d); 6.10 (1H, s); 3.40 (3H, s); 3.00-2.50 (8H, m). MS TOF 572 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 14.25 min.

Example 121.
3-Amino-4-chlorobenzoyl-D-4-aminophenylglycine-N-(4-fluoro-2-methyl sulphonylphenyl)piperazinamide
1H nmr (CD3CN) 7.65 (1H, d); 7.45 (4H, m); 7.25 (2H, m); 7.15 (2H,d); 7.05 (1H, d); 6.10 (1H, s); 3.20 (3H, s); 3.00-2.50 (8H, m). MS TOF 560 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 11.90 min.

Example 122.
3-Amino-4-chlorobenzoyl-D-4-carboxamidophenylglycine-N-(4-fluoro-2-methyl sulphonylphenyl)piperazinamide
1H nmr (CD3CN) 7.70 (2H, d); 7.55 (1H, d); 7.45 (2H, d); 7.25 (2H,m); 7.20 (2H,d); 6.90 (1H, d); 6.10 (1H, s); 3.20 (3H, s); 3.00-2.50 (8H, m). MS TOF 588 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 12.18 min.

Example 123.
3-Amino-4-chlorobenzoyl-D-4-(methylcarboxamido)phenylglycine-N-(4-fluoro-2-methyl sulphonylphenyl)piperazinamide
1H nmr (CD3CN) 7.70 (2H, d); 7.55 (1H, d); 7.45 (2H, d); 7.25 (2H,m); 7.20 (2H,d); 6.90 (1H, d); 6.10 (1H, s); 3.20 (3H, s); 2.70 (3H,s); 3.00-2.50 (8H, m). MS TOF 602 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 12.70 min.

Example 124.
3-Amino-4-chlorobenzoyl-D-phenylglycine-4-methylbenzylamide
1H nmr (CD3CN) 7.55 (1H, m); 7. 35 (7H,m); 7.00 (4H,m); 5.45 (1H, s); 4.25 (2H,m); 2.20 (3H, s). MS TOF 408 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 14.61 min.

Example 125.
1-N-(3-Aminonaphth-2-oyl)-2-N-(4-methoxybenzoyl)-1,2-dia

mino-1-phenylethane

1H nmr (CD3OH) 7.70 (1H, d); 7. 60 (1H,7); 7.25 (9H,m);7.00 (2H,d); 6.75 (2H,d); 4.80 (1H, m); 4.25 (2H,m); 3.65 (3H, s). MS TOF 440 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 15.05 min.

Example 126.

3-Amino-4-chlorobenzoyl-D-4-carboxamidophenylglycine-R,S -2-methylcyclohexylamide

1H nmr (CD3CN) mixture of isomers only one recorded here 7.75 (2H, d); 7. 60 (2H,m); 7.30 (2H,m); 7.10 (1H,d); 5.55 (1H, s); 3.90 (1H,m); 3.25 (1H,m); 1.00-2.00 (8H,m) 0.50 (3H, m). MS TOF 443 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 9.18 min

Example 127.

3-Amino-4-chlorobenzoyl-D-4-carboxamidophenylglycine-2-indanamide

MS TOF 463 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 12.58 min.

Example 128.

3-Amino-4-chlorobenzoyl-D-4-carboxamidophenylglycine-S-N -benzyl-alpha-methylbenzylamide

MS TOF 541 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 15.34 min.

Example 129.

3-Amino-4-chlorobenzoyl-D-4-carboxamidophenylglycine-1-S -1-naphthylethylamide

MS TOF 5013 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 14.00 min.

Example 130.

3-Amino-4-chlorobenzoyl-D-4-carboxamidophenylglycine-3(1 -R,S-hydroxyethyl)anilide

MS TOF 443 (M+1+). Hplc (Magellan C8, Gradient 3,

water/acetonitrile/TFA) rt 11.81 min.

Example 131.

3-Amino-4-chlorobenzoyl-D-phenylglycine-cis,trans-2-aminocyclohexylamide

MS TOF 401 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 11.00 min.

Example 132.

3-Amino-4-chlorobenzoyl-D,L-2-(4-piperidinyl)glycine-N-(4-amino-2-methyl sulphonylphenyl)piperazinamide

MS TOF 552 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 11.00 min.

Example 133.

3-Amino-4-chlorobenzoyl-D,L-2-(4-N-methylpiperidinyl)glycine-N-(4-amino-2-methyl sulphonylphenyl)piperazinamide

MS TOF 566 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 10.83 min.

Example 134.

3-Amino-4-chlorobenzoyl-D,L-2-(4-N-trifluoroacetylpiperidinyl)glycine-N-(4-amino-2-methyl sulphonylphenyl)piperazinamide

MS TOF 649 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 12.63 min.

Example 135.

3-Amino-4-chlorobenzoyl-D-phenylglycine-(2-chloro-5-carboxamido)benzenesulphonamide

MS TOF 521 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 10.23 min.

Example 136.

4-Cyanobenzoyl-D-phenylglycine-1'-methyl-4,4'bispiperidinamide

MS TOF 445 (M+1+). Hplc (Magellan C8, Gradient 3,

water/acetonitrile/TFA) rt 10.13min.

Example 137.

3-Cyanobenzoyl-D-phenylglycine-1'-methyl-4,4'bispiperidinamide

MS TOF 445 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 10.23min.

Example 138.

4-Chlorobenzoyl-D-phenylglycine-N-(4-pyridyl)piperazinamide

MS TOF 435 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 12.11 min.

Example 139.

N-(4-Methoxybenzyl)-D-phenylglycine-N-(4-fluoro-2-methylsulphonylphenyl)piperazinamide

MS TOF 512 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 11.91 min.

Example 140.

1-N-(3-Amino-4-chlorobenzoyl)-2-N-(4-methoxybenzoyl)-1,2-diamino-1-phenylethane

1H nmr (CD3OH) 7.45 (2H, m); 7. 35 (3H,m); 7.20 (2H,m);7.10 (3H,m); 6.75 (2H,d); 4.80 (1H, m); 4.25 (2H,m); 3.70 (3H, s). MS TOF 424 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 14.05 min.

Assay protocols

Enzyme Inhibition assays:

Enzyme assays were carried out at room temperature in 0.1M phosphate buffer, pH7.4 according to the method of Tapparelli et al (J. Biol. Chem. 1993,268,4734-4741). Purified human factor Xa, trypsin, thrombin and plasmin were purchased from Alexis Corporation, Nottingham, UK.

Urokinase was purchased from Calbiochem, Nottingham, UK. Chromogenic substrates for these enzymes; pefachrome-FXA, pefachrome-TRY, pefachrome-TH, pefachrome-PL and pefachrome-UK were purchased from Pentapharm AG, Basel, Switzerland. Product (*p*-nitroaniline) was quantified by adsorption at 405nm in 96 well microplates using a Dynatech MR5000 reader (Dynex Ltd, Billingshurst, UK). Km and Ki were calculated using SAS PROC NLIN (SAS Institute, Cary, NC, USA, Release 6.11) K_m values were determined as 100.9μM for factor Xa/pefachrome-FXA and 81.6μM for trypsin/pefachrome-TRY. Inhibitor stock solutions were prepared at 40mM in Me2SO and tested at 500μM, 50μM and 5μM. Accuracy of Ki measurements was confirmed by comparison with Ki values of known inhibitors of factor Xa and trypsin.

In agreement with published data, benzamidine inhibited factor Xa, trypsin, thrombin, plasmin and urokinase with Ki values of 155μM, 21μM, 330nM, 200nM and 100nM respectively. NAPAP inhibited thrombin with a Ki value of 3nM. Compounds of the invention were found to have activity in these assays.

Partial Thromboplastin Time (Prothrombin) Test Protocol

Venous blood was collected into 3.2% (0.109m) trisodium citrate vacutainer tubes at 1 volume of anticoagulant to nine volumes of blood. The blood cells were separated by centrifugation at 700g for ten minutes to yield plasma, which was frozen at 70°C until required. To perform the test, 100μl of plasma was pipetted into in a glass test tube, 1μl of test compound in DMSO was added, and allowed to warm to 37° over two minutes. 100μl of warm (37°) Manchester (tissue thromboplasin) reagent (Helena Biosciences, UK) was added, allowed to equilibrate for two minutes. 100μl of warm (37°) 25mM calcium chloride solution was added to initiate

clotting. The test tube was tilted three times through a 90° angle every five seconds to mix the reagents and the time to clot formation recorded. Data from a series of observations and test compound concentrations are analysed by a SAS statistical analysis program and a CT2 (Concentration required to double clotting time) for each compound is generated.

Compounds of the invention were found to significantly elongate the partial thromboplastin time (Prothrombin time).

Example No.	Conc. necessary to double the prothrombin time (μM)[a]
9	26
37	6.7
42	7.8
44	11
47	8.8
50	9.0
51	12
52	12
74	8.6
75	2.1
76	4.4
77	6.1
78	1.4
80	3.6
81	5.8
82	4.0

[a] The concentration quoted is that of the solution which, when added to the other reagents in the assay, doubles prothrombin time. The final concentration in the assay mixture is one third of this value.

Compounds of the invention were found to be potent inhibitors of factor Xa.

MW

PCT GB 00 02302

Martin A Hay

30/6/2000